PB86-137163

Epidemiology and Air Pollution

(U.S.) National Research Council, Washington, DC

Prepared for

Environmental Protection Agency, Washington, DC

Oct 85

U.S. Department of Commerce
National Technical Information Service
NTIS

PB86-137163

EPIDEMIOLOGY AND AIR POLLUTION

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No.
4. Title and Subtitle Epidemiology and Air Pollution			5. Report Date October 1985
			6. PB86 137165/AS
7. Author(s)			8. Performing Organization Rept. No.
9. Performing Organization Name and Address National Research Council Commission on Life Sciences 2101 Constitution Avenue, N.W. Washington, DC 20418			10. Project/Task/Work Unit No.
			11. Contract(C) or Grant(G) No. (C) 68-02-4073 (G)
12. Sponsoring Organization Name and Address U.S. Environmental Protection Agency			13. Type of Report & Period Covered Final
			14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This report explores the scientific feasibility of conducting epidemiologic investigations of the health consequences of current and future air pollution. It assesses the limits of available epidemiologic techniques for studying air pollution problems and discusses opportunities for expanding these limits and for using epidemiologic studies effectively in an overall program of research on air pollution.

17. Document Analysis a. Descriptors

Epidemiology, research, air pollution, air pollutants, carbon monoxide, lead, sulfur oxides, nitrogen oxides, particulates, health effects, exposure

b. Identifiers/Open-Ended Terms

Epidemiology, research, air pollution, air pollutants, carbon monoxide, lead, sulfur oxides, nitrogen oxides, particulates, health effects, exposure

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
This report has been approved for public sale; its distribution is unlimited.	unclassified	
	20. Security Class (This Page) unclassified	22. Price

(See ANSI–Z39.18)

See Instructions on Reverse

OPTIONAL FORM 272 (4–77)
(Formerly NTIS–35)
Department of Commerce

EPIDEMIOLOGY
AND
AIR POLLUTION

Committee on the Epidemiology of Air Pollutants
Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C. 1985

231

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The National Research Council was established by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and of advising the federal government. The Council operates in accordance with general policies determined by the Academy under the authority of its congressional charter of 1863, which establishes the Academy as a private, nonprofit, self-governing membership corporation. The Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in the conduct of their services to the government, the public, and the scientific and engineering communities. It is administered jointly by both Academies and the Institute of Medicine. The National Academy of Engineering and the Institute of Medicine were established in 1964 and 1970, respectively, under the charter of the National Academy of Sciences.

The study reported in this publication was conducted at the request of and funded by the U.S. Environmental Protection Agency under Contract 68-02-4073.

Illustrations: Cover, Dr. Clarence C. Gordon, (c) National Geographic Society; page 20, Jodi Cobb, (c) National Geographic Society; page 36, Dr. Arnold Brody, National Institute of Environmental Health Sciences; page 88, Dr. Clarence C. Gordon, (c) National Geographic Society; page 126, Jodi Cobb, (c) National Geographic Society; page 162, Martin Rodgers, (c) National Geographic Society; page 190, Barrie Day School.

Available from: National Academy Press, 2101 Constitution Ave., N.W., Washington, D.C. 20418.

Committee on the Epidemiology of Air Pollutants

MAUREEN M. HENDERSON, *Chairman*, Department of Epidemiology, University of Washington, Seattle, Washington
PHILIP J. LANDRIGAN, *Co-Vice-Chairman*, Environmental Sciences Laboratory, Department of Community Medicine, Mt. Sinai Medical Center, New York, New York
PAUL D. STOLLEY, *Co-Vice-Chairman*, Clinical Epidemiology Unit, University of Pennsylvania, Philadelphia, Pennsylvania
JOHN C. BAILAR, III, Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, and Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, D.C.
DAVID V. BATES, Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada
INGE F. GOLDSTEIN, Division of Epidemiology, School of Public Health, Columbia University, New York, New York
ROGENE HENDERSON, Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico
MARVIN S. LEGATOR, Division of Environmental Toxicology, Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas
PAUL J. LIOY, Institute of Environmental Medicine, New York University Medical Center, New York, New York
SAMUEL C. MORRIS, Department of Energy and Environment, Brookhaven National Laboratory, Upton, New York
PAUL R. PORTNEY, Resources for the Future, Washington, D.C.
CARL SHY, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina
JOHN D. SPENGLER, Department of Environmental Science and Physiology, Harvard School of Public Health, Boston, Massachusetts
BAILUS WALKER, Department of Public Health, The Commonwealth of Massachusetts, Boston, Massachusetts

National Research Council Staff

PETER H. GANN, Project Director
DEVRA LEE DAVIS, Executive Director, BOTEHH
MARY ELLEN SCHECKENBACH, Staff Assistant
JAMES LANEAR, Administrative Secretary
NORMAN GROSSBLATT, Editor
BARBARA MANDULA, Consultant

Board on Toxicology and Environmental Health Hazards

GERALD N. WOGAN, *Chairman*, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

DONALD HORNIG, *Co-Vice-Chairman*, Harvard School of Public Health, Boston, Massachusetts

PHILIP J. LANDRIGAN, *Co-Vice-Chairman*, Environmental Sciences Laboratory, Department of Community Medicine, Mt. Sinai Medical Center, New York, New York

JOHN DOULL, Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas

HERMAN N. EISEN, Department of Biology and Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts

EMMANUEL FARBER, Department of Pathology, University of Toronto, Toronto, Ontario, Canada

RICHARD MERRILL, School of Law, University of Virginia, Charlottesville, Virginia

EMIL PFITZER, Department of Toxicology and Pathology, Hoffmann-La Roche Inc., Nutley, New Jersey

LIANE B. RUSSELL, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee

ELLEN SILBERGELD, Toxics Program, Environmental Defense Fund, Washington, D.C.

PETER SPENCER, Institute of Neurotoxicology, Albert Einstein College of Medicine, Bronx, New York

Ex Officio

ROY E. ALBERT, Institute of Environmental Medicine, New York University Medical Center, New York, New York

GARY P. CARLSON, Department of Pharmacology and Toxicology, Purdue University School of Pharmacy and Pharmacal Science, Lafayette, Indiana

THOMAS CHALMERS, Mt. Sinai Medical Center, New York, New York

ARTHUR B. DUBOIS, John B. Pierce Foundation Laboratory, Yale University, New Haven, Connecticut

ALAN M. GOLDBERG, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland

MAUREEN M. HENDERSON, Department of Epidemiology, University of Washington, Seattle, Washington

ROGER O. McCLELLAN, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico
DANIEL B. MENZEL, Department of Pharmacology, Duke University Medical Center, Durham, North Carolina
NORTON NELSON, Institute of Environmental Medicine, New York University Medical Center, New York, New York

Board Staff

DEVRA LEE DAVIS, Executive Director
JACQUELINE PRINCE, Staff Associate

Acknowledgments

Many persons provided the Committee and staff with helpful information, suggestions, and the benefits of their experience during preparation of this report. We wish especially to express our gratitude for contributions made by Edward Baker, Roger Detels, Jack Hackney, Carl Hayes, Kaye Kilburn, Brian Leaderer, Samuel Marcus, Jean McRae, Rene Mendes, Paul Morrow, Marvin Schneiderman, Kirk Smith, and Warren Muir. We also wish to thank Barbara Mandula, who helped organize the project in its early stages and contributed substantially to its completion; Danny Kao and Christopher Wendel, who also helped finish it; Edna Paulson and Victor Miller, of the Toxicology Information Center, who provided continual access to the literature; and Gunther Craun, of the Environmental Protection Agency (EPA), our project officer. Devra Lee Davis, Executive Director of the Board on Toxicology and Environmental Health Hazards, provided valuable assistance in review throughout this project, and Alvin G. Lazen, Executive Director of the Commission on Life Sciences, offered much helpful advice. Without the support of Bernard Goldstein and Roger Cortesi of EPA, the project would not have been possible. Without the editorial work of Norman Grossblatt, it would have been a great deal more difficult to read about; he edited the entire report with the utmost degree of efficiency and professional judgment.

Finally, the extraordinary skill and unselfish dedication of James Lanear and Mary Ellen Scheckenbach were evident to all who witnessed or participated.

Preface

The Committee on the Epidemiology of Air Pollutants dealt with a difficult charge under severe time constraints. That it completed its task well and on time is a credit to both its members and its dedicated and outstanding National Research Council scientific staff colleagues. Dr. Peter Gann in particular assumed major responsibility for coordinating, translating, and negotiating ideas, opinions, and insights among and between Committee members, consultants, and responsible NRC executives.

The Committee's report is about epidemiology, but is not written for epidemiologists. It is a written answer to a specific charge from EPA administrators. In the Committee's view, the report to the EPA administrators is likely to be of interest to a much wider audience of federal and state air pollution control program directors, as well as to a variety of scientists concerned with air and industrial pollution questions. These scientists will mostly be in other scientific disciplines and have a need either to work with epidemiologists or to use epidemiologic strategies.

The Committee members met and shared a wide variety of opinions about the match between pertinent air pollution research questions and current epidemiologic concepts and strategies. These individuals had been chosen for their diversity of expertise, experience, and opinions, and they devised a work plan that would use this diversity to full advantage.

The Committee established a common base of state-of-the-art knowledge through the circulation and discussion of background papers prepared by its own experts. It then implemented its functional plan that depended upon meetings of small ad hoc working groups of members. These interdisciplinary working groups developed conceptual and operational approaches to assigned segments of the work at hand. The work was carried out in three phases, which moved from the most general to the most specific subject matter and from development of consensus to the preparation of the first drafts of chapters of the report.

The composition and leadership of the groups were deliberately changed as work progressed. Every effort was made to concentrate attention on critical issues and ideas that had not been fully explored or reviewed in the recent literature and to avoid either discussing or writing about subjects for which good recent reviews were available. Some of the Committee's working concepts and guidelines mentioned in the report itself are worth highlighting here.

It concentrated on long-term respiratory morbidity in relation to ambient air pollution. This was an expedient choice based on past and present research priorities and without reference to any changes in the relative importance of short-term respiratory effects and short- and long-term effects in other organ systems as smoking habits change. It concerned itself more with public than with personal health and more with morbidity than with mortality. This was another decision taken to expedite and focus the Committee's effort. It does not imply that clinical observations and mortality data should be disregarded by future investigators.

The full Committee agreed upon the most important research questions in air pollution and used them to test the practicality of its conclusions and recommendations. Some of this work is included in the report to illustrate ways in which epidemiologic methods can be applied to current air pollution research questions.

The Committee's conceptual approach is a little different from the usual. It used a working concept of ambient air as "the air breathed in 24 hours" and ambient pollution as "the pollutants in breathed air." In its thinking, it did not try to separate that part of the air breathed in and out each day by an average man or woman that comes from indoor, outdoor, or occupational sources. This definition accepted a very heterogeneous exposure to pollutants, pollutant mixtures, and their concentrations. The synergistic as well as additive effects of mixtures of pollutants were an important facet of this heterogeneity. Another working concept made explicit by the Committee is that irritants like cigarette smoke reach the lungs in the medium of breathed air, which can potentiate or reduce their biological impact. A public health perspective is maintained throughout the report with reference to attributable risk and to effects that are harder to distinguish among individuals than among populations. Finally, the Committee conducted its own deliberations about research strategies and methods keeping in mind total sources of bias in any epidemiologic air pollution research project.

The report itself was prepared and edited by Committee members before it was sent to consultants and reviewers. The distributed responsibilities for writing put an additional burden on the entire staff of the Committee. The report could not have been completed in time without their uniform and continual responsiveness and patience.

Maureen Henderson
Chairman
Committee on the Epidemiology
of Air Pollutants

Contents

Executive Summary 1

1 **Introduction** 21

2 **Assessment of Health Effects** 37

3 **Exposure Assessment** 89

4 **Concepts and Strategies in Planning Epidemiologic Studies on Air Pollution** 127

5 **The Application of Epidemiology to Selected Research Questions** 165

6 **Conclusions and Recommendations** 191

Appendix A Morbidity and Mortality From Respiratory Disease in the United States 202

Appendix B National Ambient Air Quality Standards 204

Appendix C Pitfalls in Design, Analysis, and Interpretation 205

COLOR ILLUSTRATIONS REPRODUCED
IN BLACK AND WHITE

Executive Summary

This most excellent canopy, the air, look you,
this brave o'erhanging firmament, this
majestical roof fretted with golden fire--why,
it appears no other thing to me than a foul
and pestilent congregation of vapours.
Hamlet, Act II, Scene 2

INTRODUCTION

This report responds to a request by the Environmental Protection Agency (EPA) that the National Research Council consider the scientific feasibility of conducting epidemiologic investigations of the health consequences of current and future air pollution. In particular, the Research Council was asked to:

- Identify physiologic changes and adverse human health consequences (acute and chronic) that might be associated with air pollutants and that require additional study.

- Identify existing exposure monitoring methods that can be used in epidemiologic studies and situations for which such methods need to be developed or improved to permit epidemiologic studies to be more useful.

- Determine the types of epidemiologic studies and research strategies that are needed for assessing health effects of exposure to air pollutants.

- Identify populations and exposure conditions that merit additional epidemiologic study to determine health effects of air pollution.

To address those and related issues, the Research Council formed the Committee on the Epidemiology of Air Pollutants in the Board on Toxicology and Environmental Health Hazards of the Commission on Life Sciences. The Committee consists of professionals in a variety of fields, including epidemiology, toxicology, atmospheric science, clinical research, biostatistics, risk assessment, and economics.

The subject of the Committee's report is epidemiology and its methods as applied to air pollution health effects. The primary goal of epidemiologic studies of air pollution is to relate health outcomes in human populations to quantities and types of contaminants in the air. During recent years, there have been major changes in the factors that influence such studies, such as the magnitude of the effects of exposure relative to background disease rates, the general magnitude of exposure to air pollution, and the strength of epidemiologic tools available. This report assesses the limits of available epidemiologic techniques for studying air pollution problems and discusses opportunities for expanding these limits and for using epidemiologic studies effectively in an overall program of research on air pollution.

Outdoor concentrations of many air pollutants--such as sulfur dioxide, particles, ozone, and lead--over most of the United States have decreased during the last 20 years. Widespread serious, even lethal, episodes of acute illness due to ambient air pollution were once common, but are no longer expected. In general, attendant health problems are likely to be less numerous and less severe--and therefore more difficult to detect--than in the past. However, the current picture also includes locally high concentrations, changing patterns of pollutant dispersion (due in part to recent control measures), and recognition of new pollutants, including those found indoors. Continued efforts to detect and describe the health effects of air pollution are needed, because small or infrequent effects spread over large populations can have important public health consequences, because air pollution sometimes acts in synergy with other agents to cause or exacerbate serious disease, and because the effects of past control measures are not all well understood.

Epidemiology as a discipline has a special role in the formulation and evaluation of preventive strategies. It can detect hazards in populations under actual exposure conditions, determine the magnitude of their impact on public health, and provide direct guidance for intervention. One of the major challenges for future studies is to assess exposure, particularly to individual pollutants or classes of pollutants, with enough precision to permit quantitative estimation of risk. Such assessments must take into account indoor as well as outdoor exposure. Assessment of the health effects themselves poses technical challenges, because each disease known to be caused by air pollution has other causes as well. All the diseases of concern are believed to be multifactorial, and in most cases our knowledge regarding pathophysiology is sparse. Numerous factors other than air pollution can influence the risk of illness, and these must be accounted for if causal relationships between air pollution and disease are to be clearly established. Some new and better research techniques have been developed, and some are under development. These advances (and the advantages of experience) make it likely that future epidemiologic studies can contribute to further reduction of air-pollution-related illness.

HEALTH EFFECTS

The Committee finds that evidence from controlled human exposures, toxicology, and epidemiology is sufficient to warrant concern that current air pollution still produces substantial adverse health effects in some segments of the U.S. population. These effects include a variety of acute and chronic respiratory problems that have been linked with previous kinds and amounts of pollution. Acute respiratory effects of concern include an increase in the frequency of asthmatic attacks, transient deficits in pulmonary function, and increases in the frequency of respiratory disease in children and adults. Future pulmonary research to clarify the basis for individual variation in response and determine the relation between acute effects and long-term lung function will be particularly important in defining new opportunities for epidemiologic study of air pollution and acute effects.

Chronic effects that warrant study include chronic obstructive pulmonary disease (COPD)--a broad term that encompasses emphysema, bronchitis, and some other conditions in which there is limitation of airflow in the lungs--and adverse changes in the rate of growth or reduction of lung function. Some of these effects in the U.S. population have been caused by heavy pollution exposure over sustained periods in the past; evidence on possible chronic respiratory effects of current pollution is sparse, because of methodologic difficulties and a dearth of recent studies. As gaps in the natural history of chronic airflow obstruction are filled, some constraints in studying the role of air pollution in that complex syndrome will be relaxed.

The Committee also finds important research questions about the epidemiology of lung cancer. The contribution of air pollution to the lung-cancer burden and, in particular, the interaction of air pollution with cigarette smoking require further exploration.

Some of the nonrespiratory effects that warrant further epidemiologic study are the effects of lead on childhood neurobehavioral development and on blood pressure and the effects of carbon monoxide on ischemic heart disease. Possible carcinogenic, mutagenic, or neurotoxic effects of community exposures to benzene and other volatile organic substances are also of concern, but full-scale epidemiologic studies might not yet be feasible except in selected areas near point sources.

Traditional tools for measuring health effects in epidemiologic studies of air pollution include routine collection of morbidity and mortality data, questionnaires, and spirometry. The availability of FEV_1 and other simple, noninvasive measures of pulmonary function has greatly benefited cross-sectional and longitudinal epidemiologic studies of respiratory disease. Refinements and standardization procedures in the use of these older tools can improve study sensitivity. Some newer techniques in pulmonary function testing, such as airway-reactivity challenge, expand the range of measurement capabilities and might provide important opportunities to study new end points.

Biologic markers in such readily obtained biologic samples as blood, urine, and sputum can reveal evidence of exposure or disease in early stages and will find increasing application in epidemiologic studies of air pollution effects. These markers will be needed to provide information on biochemical changes that precede overt changes in lung function. Such markers could also identify susceptible persons. The protease-antiprotease hypothesis in emphysema offers the most promising terrain for the development of these new tools. Immunochemical methods are already capable of detecting extremely small quantities of connective-tissue breakdown products in biologic fluids. Current research on the sources of variation in these measurements and their predictive value will determine their feasibility for use in epidemiologic research on air pollution.

EXPOSURE ASSESSMENT

The assessment and measurement of exposure are important and difficult aspects of the design and conduct of epidemiologic studies of air pollution. "Exposure assessment" refers to a set of multidisciplinary activities that describes who is exposed to how much of what substances, for how long, and under what conditions. Whether based on direct measurements or on modeling, exposure assessment is a vital part of environmental epidemiology. Air pollutants do not occur independently, but rather as mixtures of natural, industrial, transportation, and residential exposures; hence, assessment of exposure to air pollutants is particularly complex. The Committee considered assessment of exposure relevant to human health and did not examine exposure relevant to potential environmental damage.

Most epidemiologic studies of air pollution have assumed that exposure, however measured, constitutes an adequate surrogate of the dose of a given pollutant. Recent advances in toxicology and molecular epidemiology have emphasized some important distinctions: "exposure" refers to a concentration of a pollutant measured in the environment, "internal dose" is the amount of a substance or its metabolites in body tissues, and "biologically effective dose" is the amount of a substance that interacts with a particular target tissue or its surrogate. Information on internal dose and biologically effective dose is not generally available, but should be developed. In the interim, epidemiologic studies of air pollution will continue to rely on outdoor and indoor ambient exposure data, including data based on personal monitoring.

Today, air pollution monitoring is a highly developed field of applied science, with sophisticated analytic devices for measuring many contaminants, both indoor and outdoor. However, advances in measurement technology do not in themselves provide a valid rationale for a given study. Many studies that are possible might be unimportant or of unlikely productivity.

With present knowledge, air pollutants can be divided into three categories of sources: outdoor, such as sulfates, ozone, and lead; outdoor and indoor, such as fine particles, nitrogen oxides, and carbon monoxide; and indoor, such as volatile organic compounds, radon and its progeny, formaldehyde, and woodsmoke. In reviewing the physical, chemical, and biologic characteristics of pollutants, the Committee noted that some emissions are "fresh" (from local sources) and some "aged" (from distant sources). The Committee identified and assessed some pollutants of concern, including "older" pollutants (some of which are regulated), such as acid aerosols, ozone, nitrogen dioxide, carbon monoxide, lead, and radon and its progeny. Emerging classes of pollutants that might require epidemiologic and exposure studies include volatile organic compounds and products of incomplete combustion.

Documentation of the importance of indoor concentrations of pollutants is profoundly altering air pollution epidemiology. More than two-thirds of the time of the average U.S. citizen is spent indoors. Therefore, the presence of even moderate amounts of pollutants indoors can influence the classification of a person with regard to pollutant exposure. A goal of exposure assessment in epidemiologic studies of air pollution is to minimize the misclassification of study subjects by exposure magnitude or type. To this end, further development of integrated exposure assessment will be vital for air pollution epidemiology. The Committee recognizes that total personal exposure to an air pollutant is a conceptually important measure for epidemiology, in that it provides the most valid overall predictor of the risk of any air-pollution-related health effect. Several factors that can modify personal exposure might also be relevant in planning exposure assessment for epidemiologic studies, including activity, respiratory tract physiology, and weather patterns. Many of the established air pollution monitoring networks were not originally designed to represent personal exposure or to test explicit biologic models that considered such factors.

Future epidemiologic studies of air pollution will often require selective use of more accurate quantitative measures of exposure (such as personal monitors) than have been used in the past, if they are to link exposure to disease. In particular, the usefulness of central monitoring station data to represent individual exposure will be limited. Where the effects studied are common and the risks of developing an effect are low but important, minimizing the misclassification of exposure will be necessary to increase the chance of finding differences between groups exposed to different extents. Research is needed to characterize pollutants and to validate the use of surrogate measures. Exposure assessment data can be used during study planning to improve several aspects of study design, including selection of study populations, specification of the relevant physical, chemical, or biologic characteristics of pollutants, and determination of needed sample size.

CONCEPTS AND STRATEGIES IN PLANNING EPIDEMIOLOGIC STUDIES ON AIR POLLUTION

Success in protecting the public from very high exposures to air pollution has fostered a situation in which both research questions and research strategies to address them must be more focused and more precise than in the past, when both exposures and effects were more apparent. Specification of the details of a research question--including type of exposure, temporal features, health effect of concern, population at risk, and known risk factors aside from air pollution--is a vital part of study planning.

Several different types of research questions regarding air pollution can be addressed epidemiologically. Some pose greater inherent difficulty than others and necessitate more restricted answers. In general, questions involving dose-response relations at low doses or thresholds for chronic effects are the most severely constrained. Advances in these matters will depend largely on the development of more sensitive tools for measuring both exposure and effect. Questions that deal with attributable risk (the proportion of a given effect in a population that is due to air pollution) are uniquely appropriate for epidemiology and should play a larger part in future research.

The importance of specifying research questions cannot be overemphasized. Furthermore, to provide credible estimates of low risks, epidemiologic studies will require attention at all stages to all potential sources of error; the Committee discussed a few concepts relevant to managing potential sources of error, with particular attention to air pollution studies. Another factor that has become an integral part of epidemiologic research planning concerns estimating the cost-effectiveness of various ways to answer specific questions.

Epidemiologic methods that could be applied to air pollution questions include descriptive epidemiology or univariate studies; ecologic studies; cohort studies; case-control methods, including the nested case-control method; cross-sectional studies; and intervention studies. Case-control studies are generally quicker and less expensive than longitudinal studies, but have been used only infrequently for air pollution effects, partly because it is difficult to reconstruct past exposures with adequate precision. Prospective longitudinal studies based on individual measurements of exposure and effect are likely to provide the strongest basis for epidemiologic inference on air pollution, but they might take years of observation, are generally expensive, and often require a tradeoff between sample size and duration of followup. Cross-sectional studies, in which exposure and effect data are collected concurrently during a single period, can also be useful for studying air pollution effects under some circumstances.

Epidemiologists can develop productive studies on air pollution by taking advantage of several different types of special (and sometimes transient) situations. Analogous exposures in the workplace, migrant populations, pristine environments, and highly polluted areas overseas might provide opportunities to circumvent various methodologic constraints.

Development of productive epidemiologic strategies in a difficult field like air pollution research will require time, organization, and patience. Necessary characteristics of the milieu for such research include opportunities for interaction among epidemiologists, clinicians, and toxicologists; provisions for training and career development of new scientists; opportunities for assembling multidisciplinary research groups; stable administrative and financial support; adequate overall funding; and an appropriate range of contact with government personnel.

APPLICATION OF EPIDEMIOLOGY TO SELECTED RESEARCH QUESTIONS

The Committee uses epidemiologic approaches to selected questions in air pollution research to illustrate the points made in its report. Using a framework that considers critical components of study strategy and design, the Committee addresses questions involving four health effects of concern: acute respiratory infection, chronic obstructive pulmonary disease (COPD), asthma, and lung cancer. The same framework is applied to the study of five types of pollutants likely to be of continuing concern in the United States: woodsmoke, nitrogen oxides, persistent ozone and acid aerosols, episodic ozone and acid aerosol haze, and radon.

The illustrated approaches use a range of study methods and several ways of measuring exposure and effect variables and identifying opportunities for study. For example, effects of air pollution on upper respiratory infections in children under the age of 2 seem to lend themselves to relatively straightforward prospective study; the end point is common, and the exposure history reasonably reliable, although the researcher needs to be especially concerned with indoor pollutants. Case-control studies of specific outcomes, such as acute bronchiolitis in infants, would not require prohibitively large numbers of subjects. Study of some acute effects or episodic exposures--such as asthmatic attacks, exacerbations of chronic lung disease, and exposure to ozone and acid aerosol haze--might be approached with small panels of subjects and individual regression models for each subject based on the probability of an adverse event on a given day.

Research to understand air pollution and the origin of COPD will require great care and ingenuity. The occurrence of new cases of COPD is relatively infrequent, so prospective studies of the role of air pollution in the etiology of this syndrome would be infeasible, owing to cost and time considerations. One could instead study the onset of COPD retrospectively or study the development of early physiologic or biochemical markers that presage the onset of the complete disease. The latter strategy is limited at present by gaps in our understanding of the natural history of COPD. All retrospective methods for studying this subject, however, will suffer from the lack of reliable, precise data on individual lifetime exposure to ambient pollutants. Rate of decline in such lung-function measurements as the FEV_1 currently are the most sensitive relevant markers for COPD; in this approach, desirable samples for cohorts are smaller than might be expected, and small samples could be used to study persistent exposures to such pollutants as ozone and acid aerosol. Large multicenter case-control studies and the use of short-term indicators of mutagenic and carcinogenic effects are feasible, although not necessarily easy, for the study of the relation of air pollution and lung cancer. An unusually large cohort like that under study by the American Cancer Society might also present opportunities for prospective study.

For studying the effects of woodsmoke, ecologic studies might be especially helpful initially, whereas indoor monitoring is crucial for studying the effects of nitrogen dioxide. In some studies of air pollution effects, it might be useful to eliminate direct smoking as a confounder by restricting study subjects to nonsmokers; however, only by including smokers can interactions between air pollution and smoking be detected.

CONCLUSIONS AND RECOMMENDATIONS

Results of well-conducted epidemiologic studies can provide unique and valuable information about the health effects of air pollution. In view of the primary responsibility of the Environmental Protection Agency (EPA) for determining and acting on air quality in the United States, the Committee makes the following major recommendation:

> The Environmental Protection Agency should develop a long-term plan for research on air pollution; and population-based studies, in the form of a program in epidemiology, should be an integral part of that plan.

CHARACTERISTICS OF A PROGRAM IN AIR POLLUTION EPIDEMIOLOGY

To be productive and cost-effective, the epidemiologic program should have the following four major characteristics:

- Maintenance of a capability to interpret and synthesize current knowledge about air pollution and, accordingly, to plan relevant short-term epidemiologic research and make appropriate changes in long-term research.

- Inclusion of mechanisms for the creation of multidisciplinary teams to plan and conduct population-based epidemiologic research on the adverse health effects of air pollution.

- Means of ensuring stable, long-term epidemiologic research in a context that supports the career development of the researchers and thus limits disruptive changes in personnel.

- Exploration of collaboration with agencies that collect or could collect relevant data, after careful consideration of overall long-term data needs.

A productive epidemiologic research program must have a dual character with respect to sensitivity to outside forces. Part of the program must be dedicated to responding to rapidly changing conditions that offer important opportunities for study, to the varying concerns of regulators, and to new information from technologic development and parallel disciplines. In particular, toxicology, clinical research, and epidemiology should be viewed as parts of the same framework; advances in any one can drive new efforts in the others. Another part of the program, engaged in long-term research strategies or longitudinal studies, must remain relatively isolated and free from abrupt change, although the incorporation of new elements will sometimes be desirable.

It is important that the EPA program staff at all levels include highly trained and experienced epidemiologists, regardless of whether research is conducted intramurally or extramurally. Continuous access to both advice and review from scientists outside the institution will also be needed.

Given the constraining and difficult nature of today's questions about air pollution, stable research teams with expertise in several critical fields will be most productive. Epidemiologists in the teams should collaborate with atmospheric scientists, statisticians, and health effects scientists in all phases of research, from study design through interpretation. The present structure of many universities and government research agencies often makes it difficult to arrange such collaboration. Financial and administrative mechanisms that encourage development of these teams must be implemented; and the EPA program staff itself must have a multidisciplinary composition.

The program should assess the value of large data systems developed for reasons other than air pollution studies (such as the National Health and Nutrition Examination Survey, the National Health Interview Survey, and the National Ambulatory Medical Care Survey) as resources in air pollution research. Some of them might be modified and linked to air pollution exposure data to develop a feasible and cost-effective research approach that affords very large samples. Modification in the routinely collected air sampling data alone might be appropriate, to facilitate use of these data in some types of epidemiologic studies.

THE FOCUS FOR RESEARCH

For the immediate future, the epidemiologic research program should focus on the following exposures and effects of concern:

- Persistent air pollution problems, including the health effects of acid sulfate particles, ozone, nitrogen dioxide, carbon monoxide, lead, and radon. It should be flexible enough to address emerging problems, such as the health effects of products of incomplete combustion and volatile organic chemicals.

- Lung disorders in which air pollution might play a role, including chronic obstructive pulmonary disease, asthma, decreased rate of lung growth or increased rate of lung decline with aging, and increased susceptibility to acute respiratory infections.

- The quantitative contribution of air pollutants to lung cancer in human populations. For this purpose, it could take advantage of the existing funding arrangement between EPA and the National Cancer Institute for the support of epidemiologic studies of this problem.

Many important questions about the "traditional" pollutants remain unanswered. For example, the acute and chronic respiratory effects of acid aerosol and ozone exposures, which might result only from outdoor sources, are not well understood. A large population, perhaps in excess of 100 million, is exposed to ambient ozone at high concentrations during the spring and summer. Shifts in coal combustion to the south central states will result in an increase in the area and population exposed to acid aerosols. No systematic epidemiologic study has been designed to assess either the acute or chronic effects of this type of shift in exposure. Exposures to acid aerosols are likely to increase more in rural areas than in urban areas, so consideration should be given to locating baseline and followup studies in rural areas.

As new automotive fuels, new industries, new fuel sources, new commercial products for the home, and new building ventilation patterns are introduced, they might yield new pollutants and pollution patterns that require epidemiologic evaluation. These changes will result in increased exposures to volatile and particulate organic compounds, radon, carbon monoxide, and other potentially hazardous materials.

Indoor air pollution can be a major factor--in some instances the principal factor--in determining total personal exposure (averaged and acute) to air pollutants. Epidemiologic studies must therefore consider indoor or outdoor concentrations, or both, depending on the health response and pollutant being examined. For example, average and peak exposures to nitrogen dioxide are determined primarily by the presence of unvented indoor combustion sources. Peak exposures higher than those in most urban outdoor environments occur often in residences that use unvented gas or kerosene as a cooking or heating fuel. Therefore, to assess the health effects of nitrogen dioxide, EPA should study respiratory infection, pulmonary function changes, and, as soon as possible, biochemical indicators in association with indoor exposures and simultaneous outdoor exposures.

There have been important advances in air monitoring instruments and inferential data analysis techniques. Air pollution is a complex mixture of gases, vapors, and particles; epidemiologic studies will often benefit from detailed characterization of its components. For instance, the chemical composition and acidity of size-fractionated particles should be characterized where appropriate. In some cases, new techniques for biologic characterization are also appropriate. Detailed characterization can help to determine the air pollution components most closely associated with health outcomes, potential confounders, and the relative contributions of various sources.

The most readily observed health effects of air pollution are in the respiratory system. The proportion of the overall disease burden from common respiratory diseases that are attributable to air pollution has not yet been established. This part of the disease burden includes both the development of disease de novo and the exacerbation of pre-existing disease.

Air pollution might have nonrespiratory effects that, although not emphasized in this report, also deserve study. These include neurobehavioral deficits and essential hypertension related to lead exposure, ischemic heart disease related to carbon monoxide, and carcinogenesis and mutagenesis related to various volatile hydrocarbons.

Respiratory cancers, which are the most common cause of cancer death in men and will soon be in women, are attributable largely to cigarette smoking. However, attempts to assign proportions of this disease burden to separate causal agents, such as air pollution, are frustrated by the multifactorial and interactive etiology of these cancers. It is particularly important to understand the role of air pollutants in lung cancer, inasmuch as interactive effects might multiply the number of cases that could be prevented by reducing exposures.

The limits of an epidemiologic research program depend on the questions under consideration. Only by considering each research question carefully can one understand the limits of investigative methods and discuss them productively. In general, studies of chronic health effects are more difficult than studies of acute effects. The major problems include uncertainties in measurements of long-term exposure, the relative rarity of chronic diseases (which strains statistical power), and limitations in our understanding of the biology underlying the gradual evolution of chronic damage. Epidemiologic studies can show whether exposure to a complex pattern of polluted air increases the risk of adverse health effects in human populations, but studies are often limited in their ability to delineate the quantitative relationships between concentrations or sources of specific air pollutants and health. Such delineation requires interpretation of epidemiologic data in conjunction with toxicologic and clinical research.

Susceptibility to the effects of air pollution varies widely; studies that focus on sensitive subgroups, necessary in themselves, are an important part of strategies to detect and measure the effects of air pollution in the general population. The sensitive-subgroup approach to increasing the effectiveness of air pollution epidemiology must be furthered by broad-based efforts (toxicology, clinical research, and epidemiology) to clarify the precise nature and degree of sensitivity of such groups as the young, the elderly, those with increased airway reactivity, and those with particular preexisting diseases. Opportunities for carrying out epidemiologic studies on populations exposed to unusual magnitudes or patterns of air pollution must be specifically sought. By circumventing various methodologic constraints, these studies might provide information that would not otherwise be easily obtained. The opportunities include the use of occupational cohorts exposed to high concentrations, groups living in pristine environments or in highly polluted environments, and groups subjected to marked temporal changes in pollution. Collaboration with researchers in other countries might be necessary.

NEW RESEARCH TOOLS AND OPPORTUNITIES

Some constraints in air pollution epidemiology could be removed by complementary research to develop and explore the application of new tools for measuring exposure and effect. Such research and development is especially needed in two categories:

- New methods for assessing personal exposure and response to air pollution to be selectively incorporated into epidemiologic studies, with attention to the cost-effectiveness of these methods.

- Epidemiologic studies designed to determine the characteristics and the predictive value of potentially useful physiologic, biochemical, and morphologic markers of subclinical effects.

Personal exposure monitoring and modeling are sometimes needed in epidemiologic research to define study populations, optimal sample sizes, relationships of surrogate measures to exposures, and the extent of exposure misclassification associated with the use of central monitoring data. Depending on the design of a given study, only a sample of the study population might require such detailed monitoring; various strategies need to be explored and their performance documented.

Markers of physiologic, biochemical, and cellular morphologic changes will be increasingly important in air pollution studies. FEV_1, a physiologic test of lung function, has been used successfully to measure differences related to air pollution between populations. Serial measurement of FEV_1 has also proved to be sensitive and effective in following the growth and decline of lung function in large populations. In adults, a more rapid than normal decline in FEV_1 predicts premature death from pulmonary failure.

Although FEV_1 is a simple and highly reproducible test, its interpretation in terms of organ or cellular pathology is complex and subject to some judgment.

Some biochemical indicators of air pollutant exposure or early effects--such as blood lead and carboxyhemoglobin concentrations, urinary mutagens, and indexes of genotoxic damage--have already been successfully applied in population studies. Other biochemical indicators, designed to detect early pathologic processes in the lung, have recently shown promise and require further development and validation. Insights into the pathogenesis of emphysema have been particularly fruitful in opening possibilities for biochemical markers related to the breakdown of connective tissue in the lung. Development of biochemical markers for epidemiologic studies requires particular attention to constraints imposed by the need to study large groups of relatively healthy people.

Chapter 1

Introduction

1

INTRODUCTION

HISTORICAL BACKGROUND AND PURPOSE OF THE REPORT

Official registration of deaths began in England in 1837 under the supervision of William Farr, marking what many believe to be the birth of the modern era in epidemiology. The new era was only 8 years old in 1845, when analysis of the mortality data raised questions about the limitations of epidemiology in studying the problem of air pollution. The Registrar General's Fifth Report,[11] in 1845, contained the following statement:

> That smoke is irritating to the air-passages, injurious to health, and one of the causes of death, to which the inhabitants of towns are more exposed than the inhabitants of the country, is probable; but if the effect were very considerable it would be most evident in the dense fogs, when the atmosphere is loaded with smoke. . . . Now we have never observed any connection between the increase of the mortality and the London fogs.

Despite the absence of positive findings, Farr and his associates were inclined to believe that smoke in the ambient air was injurious to health. Current concerns about the role of epidemiology in the study of air pollution resemble theirs to a striking degree. Can epidemiologic studies detect the feared consequences in populations? Are these studies sensitive enough? How do we interpret apparently negative results?

These questions continue to arise because the ability of epidemiologic studies to elucidate the relationship between air pollution and health at any particular time depends on a dynamic balance among three elements: the general magnitude of exposure to air pollution, the magnitude of the effects of exposure relative to background disease rates, and the strength of the epidemiologic tools available. When infectious disease rates began to decrease in England around the middle of the nineteenth century and pollution from rapid industrialization began to increase, epidemiology became effective in demonstrating that bad air affected the public's health. In fact, its impact could be estimated reasonably accurately by counting foggy days in London and counting the excess deaths that occurred on such days.

The first two historical elements have changed enough to bring new demands on existing epidemiologic techniques, as well as a challenge to reassess their limits. This report provides such an assessment and indicates some opportunities for expanding the limits and for using epidemiologic studies effectively in an overall program of research on air pollution.

Until 1960, most epidemiologic studies of air pollution examined the impact of short-term episodes of large pollutant exposures. Studies of the air pollution "disasters" in the Meuse Valley during December 1930, Donora in November 1948, and London in December 1952 established that sudden peaks of exposure to coal combustion products and industrial pollution, superimposed on persistently high relative levels of exposure, could cause excess deaths among persons in the community who suffered from chronic cardiorespiratory diseases.[7] These epidemiologic demonstrations that air pollution can, at its worst, increase mortality due to respiratory diseases led to major clean air legislation in the United States and abroad.

In the 1960s, new problems for study began to emerge as the concerns of researchers expanded from the gross effects of short-term peaks toward effects associated with long-term, low-dose exposures. At the same time, hypotheses that called for separation of the effects of individual pollutants began to receive greater attention.

CURRENT MAGNITUDE OF OUTDOOR AIR POLLUTION IN THE UNITED STATES

The magnitude of ambient air pollution exposure might be decreasing, at least in the developed West. Data recently published by the Environmental Protection Agency (EPA) from a national monitoring survey show substantial decreases in average urban concentrations of sulfur dioxide, SO_2, carbon monoxide, CO, and lead, Pb, in the United States as a whole between 1975 and 1983.[15] Furthermore, since passage of the Clean Air Act in 1970, concentrations of total suspended particles (TSP) have also decreased substantially in many areas. The current picture is not entirely bright, however. Nitrogen oxides and ozone, O_3, have proved to be relatively harder to control. Although slight decreases in average urban concentrations of these air contaminants did occur during 1975-1983, some areas show no improvement, and O_3 concentrations actually increased by 12% from 1982 to 1983, owing to the generation of increased amounts of O_3 precursors by economic recovery and weather conditions favoring O_3 formation. Regardless of such short-term trends, exposure to some pollutants, such as O_3, might now be spread over larger populations, because of long-range transport phenomena and rapid urban growth. Other problems of increasing concern involve pollutants for which there are no standards, such as fine aerosols, sulfates, and woodsmoke. Nevertheless, in most areas of the country, the data as a whole show much progress in reducing the air pollution of the 1950s and 1960s. Therefore, we must ask what epidemiology can contribute to the study of air pollution effects that are likely to be less common and less severe than they were just 25 years ago.

MAGNITUDE OF DISEASE RELATED TO POLLUTION AND OTHER CAUSES

The second element to be considered is the magnitude of pollution-related disease relative to background disease. In Farr's day, air pollution effects might have been masked by epidemics of infectious disease; today, the effects might be masked by the predominance of cigarette smoking as a cause of respiratory disease. The impact of ambient air pollutants on the total respiratory disease burden in the United States must be small relative to the impact of cigarette smoking, and occupational exposures might also have greater effects than pollution of ambient air. The dominance of these causal factors tends to complicate the task of air pollution studies, but does not in itself eliminate the need for them. The public health importance of air pollution can be underestimated unless three points are considered:

- Air pollution might cause considerable burdens of respiratory disease, even though cigarette smoking has a greater impact. The diseases of concern are quite common. For instance, the National Center for Health Statistics estimates that in 1979-1981 there were approximately 10 million persons with chronic obstructive pulmonary disease (COPD).[16] (For more detailed information on the magnitude of respiratory diseases in the United States during recent years, refer to the tables in Appendix A.) Even if the proportion of COPD cases attributable to air pollution were low, the absolute amount of attributable disease would be high, in proportion to other public health problems. Chapter 2 presents some of the evidence that current air pollution can cause substantial health effects.

- Air pollution and cigarette smoking might have synergistic effects on the incidence of respiratory disease. Animal and epidemiologic studies suggest that air pollution exposure can multiply the risk of developing respiratory disease in smokers.[10] [17] It is also plausible that air pollution aggravates conditions caused by smoking and thus leads to increases in symptoms and other expressions of morbidity. In either case, actions taken to reduce the impact of air pollution would have the concomitant effect of preventing some smoking-related illness. (This does not suggest that efforts to reduce cigarette smoking itself should be diminished.)

- Disease related to air pollution is relatively amenable to primary prevention. Whatever the attributable disease burden, centralized intervention at the national or community level (e.g., catalytic converters, stack controls, and fuel substitution), although not simple or inexpensive, is likely to be more efficient than intervention at the level of individual behavior.

STRENGTH OF EPIDEMIOLOGIC TOOLS

The third historical element, the discriminatory potential of available epidemiologic tools, has also changed. Today, "epidemiology is no more restricted to the study of striking outbreaks of disease than meteorology is to the study of hurricanes or astronomy to eclipses of the sun."[8] New techniques and strategies have made possible more effective approaches in air pollution epidemiology, leading to studies that are substantially different from those performed in the 1960s and 1970s. Much of this report deals specifically with the capabilities and limitations of methods and strategies of the 1980s and, as well as we can foresee them, later decades.

Clean air legislation itself has begun to influence the definition of the new problems or questions for epidemiologic study. In the United States, clean air legislation is based on the view that safe or no-effect concentrations for particular categories of major pollutants can be estimated and incorporated into standards. (In contrast, such legislation in Great Britain is based on control of specific pollution sources.) Appendix B lists the current National Ambient Air Quality Standards. Epidemiologic methods are being invoked to substantiate these standards. This report discusses how this application further complicates the demands on epidemiology.

In summary, the technical demands on epidemiologic studies of air pollution are greater than ever before. Meanwhile, the cost of obtaining each additional bit of information on the new kinds of problems has increased and will continue to increase. The questions now asked can sometimes be answered only by a coalition of engineering, mathematical, and biologic scientists. The advanced technologies of these sciences, and especially their integrated use, are expensive. One of the purposes of this report is to provide decision-makers with information to assist them in planning and setting priorities for the investment of research resources.

EPIDEMIOLOGY VIS-A-VIS OTHER FORMS OF RESEARCH

Toxicology, clinical research, and epidemiology are the three disciplines that can contribute most to our understanding of the human health effects of air pollution. Each has inherent advantages and limitations in studying air pollution. Each is essential, and their complementary and interactive nature must be appreciated.

Animal experiments allow relatively precise setting of exposure conditions, control over factors that might confound observed dose-response relations, and study of a wide variety of specific end points, including effects at the biochemical or cellular level. For example, these studies have been particularly helpful in examining questions concerning the chronic effects of O_3 or nitrogen dioxide on lung structure and function. Clinical studies, which involve controlled exposure of human subjects, also offer an opportunity for precise quantification of dose and response and elimination of interfering conditions. Response to inhaled pollutants can be assessed with sophisticated physiologic techniques. These studies have provided the best means for investigation of the transient effects of pollutants in susceptible persons, such as asthmatics.

The fundamental limitation of animal experiments is the difficulty of extrapolating results from animals to humans. Furthermore, the intentional simplicity of experimental conditions, which can include exposure to only one or two pollutants, rarely simulates conditions in the natural human environment. Information obtained from clinical studies is also constrained by the need for experimental simplicity. The use of relatively few subjects inhibits generalization of results to large populations. And ethical considerations generally require that controlled-exposure studies in humans be limited to investigation of acute, fully reversible effects.

As most commonly defined, epidemiology is the study of the distribution and determinants of disease in populations. It affords a direct means of obtaining scientific information on the impact of actual air pollution on free-living human populations. Epidemiology can be distinguished from other forms of air pollution research by the special role it plays in the formulation and evaluation of preventive strategies. The discipline may be seen as, among other things, a tool for diagnosing disease in a community, rather than an individual. Furthermore, the epidemiologic perspective starts, as

Doll has said, with the 10,000 cases of disease that are present, rather than with the 10,000 chemicals that might have caused them.[2] Epidemiologic data, like data from toxicology and clinical research, can sometimes elucidate disease etiology and mechanisms, but they can also provide a clear basis and guidance for public health intervention. Knowledge of specific etiologic factors is not necessarily required. Utilizing at least 80 years of observation on the effects of London's killer fogs, health authorities chose to emphasize control of visible smoke from coal combustion before the specific agents responsible for illness could be identified.[1] The choice was propitious, inasmuch as analyses have since shown that fine particles appear to have played a greater role in causing episodic excesses in mortality than SO_2.[3] This direct use of epidemiology to develop preventive measures, without reliance on knowledge of specific causal paths, must be kept in mind in evaluating the potential contribution of epidemiologic studies of air pollution.

DIFFICULTIES IN EPIDEMIOLOGIC STUDIES OF AIR POLLUTION

Nearly all epidemiologic studies on air pollution are observational, rather than experimental. Observational studies of air pollution face several major difficulties, which are related to the three types of variables involved:

- Exposure, whether of an individual or of a population, is difficult to assess. Air pollution is a highly complex phenomenon that involves many species of pollutants undergoing continuous chemical and physical transformation. Simultaneous exposure to several major pollutants is the rule. Determining who is exposed, to what, and to how much is not easy, particularly for chronic exposure to varying concentrations.

- Effects of air pollution are difficult to assess. Earlier research on air pollution attempted to identify a "smog lesion"--the descriptive pathology of an effect peculiar to air pollution. Those attempts were fruitless, and it is now recognized that air pollution is one of many factors involved in multicausal disease processes that ultimately converge to a few pathways of organ dysfunction. Air pollution can play either a causal or an aggravating role in these disease processes.

Discerning who has suffered an effect specifically due to air pollution is not easy, nor is estimation of the extent of the effect. These tasks are all the more complicated when a chronic disease with a vague, insidious onset is considered many years after first exposure to the presumed causal agent.

- Many factors confound the exposure-effect relationship. An epidemiologic study of air pollution might be rather straightforward if it had to account only for an exposure and an effect. However, the observation that a given exposure and a given pathologic condition are found together in populations can also be explained by confounders, factors that are unevenly distributed among exposure groups and that include occupational exposure, weather conditions, pre-existing health conditions, and smoking habits. These potential confounders are numerous. Identifying them, designing studies to reduce their effects, estimating any effects that remain, and adjusting the measurement of the exposure-response relation accordingly are among the most difficult tasks in any air pollution study.

Those three fundamental problems lead to two subsidiary problems worthy of note. First, the combination of possible errors in the estimation of key variables and the need to detect a relatively small (but not necessarily unimportant) effect create a problem with respect to the sensitivity of studies. An analogy with a diagnostic tool, such as the microscope, applies here, if we think of limits to the resolving power of lenses. To discern the broad but relatively faint image of the air pollution health effect among surrounding images, epidemiologic studies must either reduce error in the estimation of variables used in the analysis (improve the optical quality of the lenses) or maintain a very large sample size (increase the magnification). When studies are insensitive, failure to see effects of air pollution cannot properly be interpreted to mean that they are not there.

The second subsidiary problem lies in the difficulty of generalizing epidemiologic results from one population to another. Because the distribution of numerous confounding factors can vary widely among populations, epidemiologic results might have only local applicability, or at least must be extended cautiously. For instance, failure to account for the existence of sensitive subgroups can distort the prediction of response in a community.

This report emphasizes the importance of specifying the research questions for which epidemiology is to provide answers. No research tool or method, however precise its measurements or powerful its inferences, can achieve much if it is applied to inappropriate questions. Generalizations regarding "air pollutants," "epidemiologic studies," "adverse health effects," or "populations" have limited utility, given the complex and diverse categories implied by each of these terms. Furthermore, questions posed for epidemiologic study must be asked in the proper form; the right question asked in the wrong way might be unanswerable.

SCOPE OF THE REPORT

The subject of this report is epidemiology and its methods; other forms of research on air pollution are discussed only as they are related to epidemiologic endeavors. The report does not address the question, "How important is air pollution?" Therefore, it does not include a complete critical review of the epidemiologic literature on air pollution. Several excellent and recent reviews are available, and the inclusion here of yet another would divert attention from issues more pertinent to the charge.[3,12-14,18] The report is also not intended as a primer on epidemiologic principles, although it discusses some specific principles related to the problems of studying air pollution. The reader should consult current textbooks on epidemiologic methods for more detailed discussion.[4-6]

Because decisions about the future control of air pollutants must be based on more sensitive end points than have generally been used in the past, we emphasize indexes of morbidity, rather than mortality. Furthermore, we stress effects on the respiratory system, because that system is the most vulnerable to the ubiquitous air pollutants and studies of respiratory morbidity encompass most of the serious questions regarding methods.

The report focuses on problems associated with common area sources of pollution, rather than those associated with point sources of contamination that occur in specific neighborhoods--hence the relative lack of emphasis on the so-called toxic air pollutants, which are currently of great concern because of, for example, the disastrous leak of chemicals in Bhopal, India. This report takes a unified approach to indoor and outdoor exposure to polluted air. Most future epidemiologic studies on air pollution should adopt a perspective that accounts for pollutant exposure in both environments. The report deals primarily with four of the EPA criteria air pollutants: SO_2, particles, nitrogen oxides, and O_3. CO and Pb, the other criteria pollutants, are given less attention, because their primary effects are not on the respiratory system and because the problems they pose for epidemiologists are quite different and generally more straightforward.

CONTENTS OF THE REPORT

Epidemiologic inquiry in environmental health involves two major steps: collection of data concerning effects, exposures, and modifying factors; and drawing of inferences from the data collected. The next two chapters deal with issues of data collection.

Chapter 2 defines the health effects that concern us and the implications of current disease models for epidemiologic studies. It also covers the various tools available for assessing effects, their constraints, the quality of data, and opportunities for the application of new tools, such as biologic markers.

Chapter 3 examines the quality of exposure data and various means for providing such data in epidemiologic studies. It emphasizes the importance of indoor air pollution and describes opportunities for improving exposure assessment. It also identifies pollutants and pollutant sources that are likely to be of interest in future studies.

Chapter 4 develops concepts and strategies appropriate to the planning of epidemiologic studies. It emphasizes the need for epidemiologists to frame their questions carefully and to consider the sources of error that can interfere with obtaining useful results. It describes the various types of epidemiologic studies and the circumstances for which they are most appropriate. It notes special opportunities for studies and discusses some aspects of the development of the proper milieu for studies and the relationship of epidemiology to regulation.

In Chapter 5, the Committee applies various designs and strategies to current research questions related to air pollution. Such questions include those on chronic and acute respiratory effects and on effects of specific air pollutants.

Some years of effort on the part of EPA and other agencies have succeeded in reducing air pollution in the United States. Nonetheless, air pollution remains a public health problem. Epidemiology can contribute to the understanding and eventual solution of this problem. Chapter 6 presents the Committee's conclusions and offers recommendations designed to optimize the epidemiologic study of air pollution.

REFERENCES

1. Ashby, E., and M. Anderson. The Politics of Clean Air. Monographs on Science, Technology and Society. Oxford: Clarendon Press, 1981. 178 pp.

2. Doll, R. Relevance of epidemiology to policies for the prevention of cancer. J. Occup. Med. 23:601-608, 1981.

3. Holland, W.W., A.E. Bennett, and I.R. Cameron. Health effects of particulate pollution: Reappraising the evidence. Am. J. Epidemiol. 110:525-659, 1979.

4. Kleinbaum, D.G., L.L. Kupper, and H. Morgenstern. Epidemiologic Research: Principles and Quantitative Methods. Belmont, Cal.: Lifetime Learning Publications, 1982. 529 pp.

5. Last, J.M., Ed. Maxcy-Rosenau Public Health and Preventive Medicine. 11th ed. New York: Appleton-Century-Crofts, 1980. 1926 pp.

6. Lilienfeld, A.M., and D.E. Lilienfeld. Foundations of Epidemiology. 2nd ed. New York: Oxford University Press, 1980. 375 pp.

7. Lipfert, F.W. Sulfur oxides, particulates, and human mortality: Synopsis of statistical correlations. J. Air Pollut. Control Assoc. 30:366-371, 1980.

8. MacMahon, B., and T.F. Pugh. Epidemiology: Principles and Methods, p. 1. Boston: Little, Brown and Company, 1970.

9. Mazumdar, S., H. Schimmel, and I.T.T. Higgins. Relation of daily mortality to air pollution: An analysis of 14 London winters, 1958/59-1971/72. Arch. Environ. Health 37:213-220, 1982.

10. Rall, D.P. Review of the health effects of sulfur oxides. Environ. Health Perspect. 8:97-121, 1974.

11. Registrar General. 5th Annual Report for the year 1843, Second Edition, p.415. London: H.M.S.O., 1945.

12. Shy, C.M., J.R. Goldsmith, J.D. Hackney, M.D. Lebowitz, and D.B. Menzel. Health Effects of Air Pollution. New York: American Thoracic Society, Medical Section of the American Lung Association, 1978. 48 pp.

13. U.S. Environmental Protection Agency. Air Quality Criteria for Oxides of Nitrogen. Publication No. EPA-600/8-82-026F. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1982. 790 pp.

14. U.S. Environmental Protection Agency. Air Quality Criteria for Particulate Matter and Sulfur Oxides. Publication No. EPA-600/8-82-029a. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1982. 204 pp.

15. U.S. Environmental Protection Agency. National Air Quality and Emissions Trends Report, 1983. Publication No. EPA-450/4-84-029. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, 1985. 112 pp.

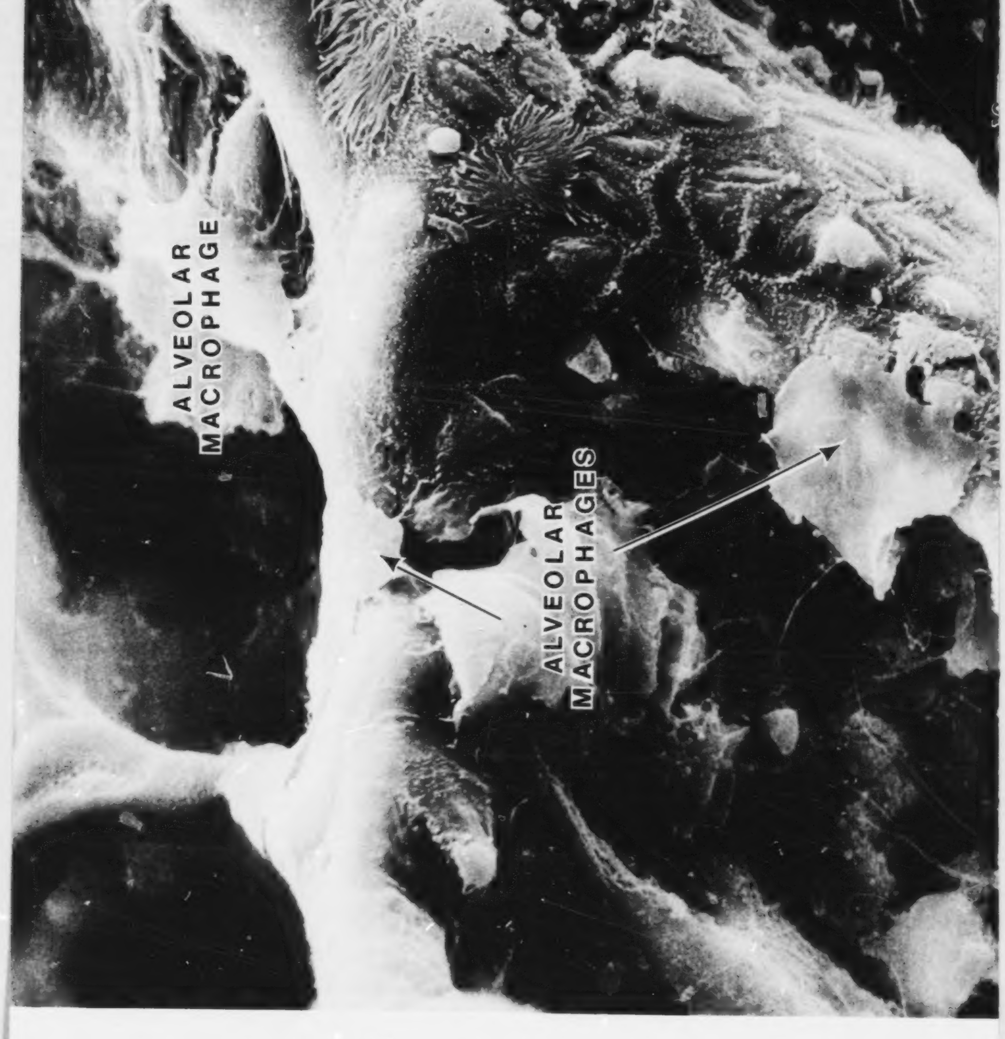
16. U.S. National Center for Health Statistics. National Health Information Survey (NHIS) unpublished data from 1979-1981. Hyattsville, Md.: U.S. Department of Health and Human Services, National Center for Health Statistics, 1985.

17. Vena, J.E. Air pollution as a risk factor in lung cancer. Am. J. Epidemiol. 116:42-56, 1982.

18. Whittemore, A.S. Air pollution and respiratory disease. Ann. Rev. Pub. Health 2:397-429, 1981.

Chapter 2

Assessment of Health Effects


ALVEOLAR MACROPHAGE
ALVEOLAR MACROPHAGES

2

ASSESSMENT OF HEALTH EFFECTS

INTRODUCTION

Epidemiologic studies usually seek to determine the relation between exposure and particular health effects. Epidemiologists use two types of measures to assess health effects: clinical data derived from medical diagnoses, often presented as rates of mortality or morbidity in established clinical diagnostic categories, such as chronic bronchitis and lung cancer; and data that reflect biologic changes that are not detected clinically. Data of the second type, sometimes called subclinical or early marker data, are obtained by measuring physiologic, biochemical, or morphologic features or by analyzing symptoms reported on questionnaires. We do not address the problem of determining exactly what constitutes an adverse health effect in an epidemiologic study, a topic recently analyzed by a Committee of the American Thoracic Society, with reference to the Clean Air Act.[1] Although annoyance or esthetic effects (such as odors or impaired visibility) undoubtedly affect human welfare, they are not discussed in this chapter, because they are not typical end points for epidemiologic study.

Biologic models of diseases and of the relationship of exposure to pathologic response, whether implicit or explicit, underlie the selection of outcome measures in epidemiologic studies. The more accurately the available models can describe, for instance, the temporal relationship of exposure to response or the reasons for variation in susceptibility, the easier it is to choose health effects data that are valid and precise.

This chapter reviews briefly some of the most important adverse health effects that might be associated with air pollution. It then discusses the various kinds of health effects data needed for future epidemiologic studies. After considering problems of data quality and availability and opportunities for improvement, it discusses how the use of these data is constrained by the incompleteness of knowledge of disease biology and by limitations in the instruments used to measure specific effects. Finally, it addresses the potential use in epidemiologic studies of biologic markers of respiratory health effects.

HEALTH EFFECTS OF CONCERN

This chapter focuses on respiratory effects, because clinical and epidemiologic studies and animal experiments have shown that the major effects of air pollutants are on the respiratory system. Health effects are divided into four categories: acute respiratory effects; chronic respiratory effects, excluding cancer; lung cancer; and effects on other organ systems.

Acute effects have a sudden onset and are relatively short-lived, lasting from a few minutes to a few days. Examples are an asthmatic attack and an exacerbation of symptoms of chronic obstructive pulmonary disease (COPD). Chronic effects persist over an extended time, generally years. Examples are a permanent respiratory loss from a decreased rate of lung growth in children and the syndrome COPD itself. These definitions of "acute" and "chronic" are somewhat arbitrary and do not provide information about the time course of antecedent exposures. For example, acute effects might be attributable to short-term fluctuations in pollutant concentrations or to cumulative exposures over an extended period. Similarly, although chronic effects are normally associated with long exposures, they can occur after single or small numbers of exposures.

Some acute effects are discrete, and others are exacerbations of chronic conditions. In most instances, the relationship of acute events to the progression of chronic disease is not well understood. In this report, "exacerbation" generally refers to an increase in frequency or severity of symptoms, without any presumption of faster progression of an underlying disease.

Attempts to relate acute and chronic health conditions to air pollution have to overcome both shared and unique types of methodologic problems. Investigators of acute effects usually suspect and examine exposures that have occurred in the previous hours or days. However, many factors that can influence the risk of illness increase and decrease with pollution (for example, temperature and photochemical oxidants), making it hard to separate the effect of air pollution itself. Chronic effects are usually related to exposure that persists over many years; even with current sophisticated diagnostic techniques, it is virtually impossible to pinpoint the onset of disease and extremely difficult to identify persons with early stages of disease.

The Committee has tried to answer two questions for each of the health effects discussed here:

- How is the adverse health effect defined and categorized? The way in which a disease process is conceptualized or modeled and the existence of gaps in knowledge of its pathophysiology and natural history have important implications for the design and conduct of epidemiologic studies.

- What evidence links the health effect to air pollution and suggests that the link is a plausible concern for the future? The purpose is not to determine whether existing evidence is conclusive, but rather to determine whether it is sufficient to warrant further study.

ACUTE RESPIRATORY EFFECTS

Asthma and Airway Hyperreactivity

Asthma is characterized by intermittent obstruction of airflow that reverts either spontaneously or with treatment. Physiologically, it is manifested by general narrowing of the air passages due to increased tone of the bronchial smooth muscle and by plugging of the airways with thick, excessive mucus. Clinical symptoms are paroxysms of shortness of breath, coughing, and wheezing. Asthma is usually an episodic disease, with acute attacks being interspersed with relatively symptom-free periods. Many asthmatics have abnormalities of pulmonary function even while symptom-free; a few, considered chronic asthmatics, are essentially always symptomatic. No standard definition of asthma for epidemiologic purposes has been established.

Approximately half of patients with asthma have atopic (allergic) asthma, which depends on an antibody response to a specific, identifiable antigen. Once sensitivity (the formation of antibodies) has developed, even minute amounts of the antigenic material induce symptoms. Many different inhalants have been identified as primary sensitizers in asthma, including large complex proteins, such as ragweed and animal dander, and low-molecular-weight synthetic chemicals, such as toluene diisocyanate.[131] Asthma that does not appear to be due to allergy to specific substances can arise from a complex set of genetic and environmental factors.

Whatever its origin, asthma is often exacerbated by a variety of nonspecific stimuli, including respiratory infection, exercise, cold air, and emotional stress. Asthmatics vary greatly in their responses to these factors, as well as in their responses to conventional forms of therapy. This heterogeneity must be considered by epidemiologists. The precision of studies will advance as groups with particular response characteristics are identified. For instance, there is evidence that some asthmatics develop prolonged responses due to inflammatory cells in the airways.[82] There is reason to believe that clarification of distinct categories will result from current breakthroughs in the understanding of biochemical mediators of airway response, such as the arachidonic acid metabolites.[52]

Air pollution can increase the risk of an attack in persons with established asthma, but it is not known whether air pollution itself is a cause of asthma. Little research has focused on the latter question. Some contemporary studies have reported increased asthmatic attack rates with greater pollution, but others have found no such correlation. Whittemore and Korn used novel statistical methods for asthma epidemiology to analyze diaries kept by a panel of 443 asthmatics in the Los Angeles area during 1972-1975.[173] The most significant predictor of attacks was the presence of an attack on the previous day. However, on the average, panelists also tended to have increased numbers of attacks on days with high oxidant and particulate pollution, on cool days, and during the first 2 months of the study.

In contrast, Goldstein and co-workers found that visits to the emergency room for asthma in New York City were more common in autumn and on Sundays and Mondays, but were not correlated with concentrations of outdoor sulfur dioxide, SO_2, or particles. They suggested that indoor exposures trigger the attacks.[55,56]

Bronchial hyperreactivity is an abnormal degree of airway narrowing in response to a stimulus that causes little or no change in normal airways. It is always present in asthma, and followup studies of workers who develop asthmatic reactions to chemicals in the workplace have demonstrated persistent bronchial hyperreactivity even after the overt symptoms of asthma ceased.[23] When apparently normal persons inhale a nonspecific bronchoconstrictor, such as methacholine, some are hyperreactive without meeting the clinical criteria for asthma.[53]

Airway reactivity seems to have a unimodal distribution; within a population, there appears to be a continuum from the most reactive to the least reactive persons, rather than a group of hyperresponders and a separate group of normal responders.[26] The health implications of airway hyperreactivity without asthma are not known, and the relationship of this state to development of other diseases, such as COPD, or to severity of respiratory infection needs further exploration.[69]

In controlled-exposure studies, somewhat surprisingly, volunteers with asthma or with COPD (subjects who, according to current disease models, would be expected to have increased airway reactivity) did not seem to be more susceptible than healthy volunteers to the effects of ozone, O_3, at low concentrations.[99,151] However, SO_2 at as low as 0.4 ppm and nitrogen dioxide, NO_2, at as low as 0.3 ppm have induced symptoms or increased airway resistance in some asthmatics undergoing heavy exercise.[14,100] Persons without respiratory disease generally do not show effects below 1 ppm.[145]

Good animal models of chronic human asthma do not exist, although acute episodes of bronchoconstriction can be induced in animals by inhalation of ambient air pollutants.[59]

Respiratory Infections and Related Effects

Upper respiratory infections include colds, influenza, and sore throats; almost all upper respiratory infections are caused by viruses. Lower respiratory infections include pneumonia and acute bronchitis, which are often caused by bacteria. Early studies clearly demonstrated a link between high concentrations of reducing pollutants--e.g., SO_2 and total suspended particles (TSP)--and respiratory infection in children.[36]

Several recent studies have shown that current concentrations of specific pollutants might also be associated with increases in respiratory infections and symptoms in exposed populations. For example, Bates and Sizto studied hospital admissions for nine respiratory and six nonrespiratory conditions at 79 hospitals in southern Ontario during January, February, July, and August in 1974, 1976, and 1978.[13] Admission data were compared with pollutant concentrations at 15 air sampling stations in the area. The strongest correlation was between concentrations of sulfates and total respiratory admissions, and the significant correlation with sulfates remained when asthma admissions were excluded from analysis.

Evidence of a relationship between acute respiratory infection and exposure to NO_2 from gas cooking stoves is suggestive, but inconsistent and inconclusive. An early report from the Harvard Air Pollution Health Study indicated an increased risk of respiratory infection before the age of 2 associated with exposure to gas cooking in the home. A later analysis, based on a larger sample, showed this risk to be still present, but no longer statistically significant.[172] In another series of studies, Melia and co-workers found a higher prevalence of respiratory infection in children aged 5-10 living in homes with gas stoves than in homes with electric stoves. This effect persisted after adjustment for parental smoking.[116]

Results of animal studies suggest that low, and sometimes brief, exposures to pollutants increase susceptibility to infection. The animal infectivity model appears to be extremely sensitive for demonstrating pollution effects. Numerous reports have shown that low concentrations of NO_2 and O_3 lower resistance of animals to bacterial infection.[38, 48, 77, 118] Such lowering has been seen in mice exposed to NO_2 at 0.5 ppm for 6 months (6 hours/day)[38] and to O_3 at 0.08 ppm for 3 hours.[118] Exercised mice were more susceptible than nonexercised mice.[77] These effects were seen at concentrations that humans might encounter, particularly during peaks of exposure. Thus, the findings could be relevant to epidemiologic studies that show more respiratory infections in areas of greater air pollution, although such infections in humans are most often viral, rather than bacterial. Animal models for studying the effect of air pollutants on susceptibility to viral agents have not yet been developed.

Transient Changes in Pulmonary Function

Pollution can cause transient changes in pulmonary function in humans both in the laboratory and under natural conditions. Changes measured in children at a summer camp include reduction in the maximal volume of air expired in 1 second (FEV_1), the peak expiratory flow rate (PEFR), and the forced vital capacity (FVC). Decrements of a few percent were found on days when O_3 concentrations were higher, particularly above 100 ppb, and an exposure-response relationship between O_3 and degree of transient change in pulmonary function tests was reported.[101] [102]

Transient effects of short-term exposures have also been demonstrated in clinical studies with healthy volunteers. O_3 has shown effects at concentrations likely to be attained in polluted air. For example, O_3 at 0.3 ppm produced symptoms of irritation of the respiratory tract and decreases in pulmonary function during 2-hour exposures of normal volunteers.[12] Avol *et al*. detected effects of O_3 at 0.16 ppm with heavy exercise,[6] and McDonnell *et al*. detected effects at 0.2 ppm.[112]

The acute response to O_3 varies greatly among individuals. Horvath and co-workers reported that FEV_1 decreased by 2-48% in 24 normal subjects exposed to O_3 at 0.42 ppm for 2 hours while they performed intermittent moderate exercise.[74] McDonnell and associates reported similar ranges.[112] McDonnell and co-workers showed that this intersubject variability is apparently intrinsic, inasmuch as it persisted over periods of months.[111]

The basis for this variation among normal subjects is unknown, but it shows that some "normal" persons can be especially sensitive to O_3 and that this sensitivity is detectable in repeated measurements. This finding has implications for the design of epidemiologic studies of air pollution, in which accurate definition of the population at risk is important.

Summary

Various components and patterns of current air pollution cause acute respiratory symptoms, including asthmatic attacks and increases in respiratory infection, especially among children. Transient decreases in pulmonary function have been seen in sensitive or exercising people exposed to O_3 and SO_2 at low concentrations. Further study is needed to understand the basis of individual variation in response and to determine whether these acute effects have a long-term impact on lung function. Whether airway hyperreactivity is related to accelerated decrease in lung function or to impairment in lung growth has not been determined. The resolution of these questions will have a direct impact on possibilities for and design of epidemiologic studies of air pollution and acute health effects.

CHRONIC RESPIRATORY EFFECTS

Three chronic effects of air pollution of great concern are the set of disorders called chronic obstructive pulmonary disease (COPD), diminished growth of lung function in children, and accelerated decrease in pulmonary function with age.

Chronic Obstructive Pulmonary Disease

The general use of the convenient, but imprecise, term chronic obstructive pulmonary disease and the widespread application of a single test of lung function, FEV_1, combine to give a false impression of simplicity to the study of this disease. The syndrome of COPD has several main components:

- Chronic mucus hypersecretion (used synonymously with "chronic bronchitis"), with hypertrophy of bronchial mucous glands and changes in small airways.[156] Its leading symptom is a chronic productive cough. Chronic bronchitis is usually ascertained in epidemiologic studies when a productive cough (one that produces sputum or phlegm) is present for at least 3 consecutive months per year for at least 2 years, provided that it is not attributable to other lung or heart disease.[68] Only in some people does chronic bronchitis lead to clinically important COPD, manifested by recurrent pulmonary infection, chronic airflow limitation, or both.

- Alveolar destruction, or emphysema. The chief symptom is breathlessness without a cough. The essential pathophysiologic element in emphysema--breakdown of alveolar walls--is apparently caused by proteolytic enzymes released by macrophages or polymorphonuclear leukocytes.[119] At present, this irreversible change in lung structure can be diagnosed with certainty only at autopsy.[157]

- Small-airway disease. This condition is seen most often as a component of COPD, but it also occurs in other diseases[105] or as a result of the inhalation of irritants. It is thought to reflect the presence of inflammation in the respiratory bronchioles.[126] Its importance as perhaps the earliest lesion in smoking-induced COPD has been recognized only recently.[72] Considerable obstruction may be present in airways smaller than 2 mm in diameter before changes in FEV_1 are detected.[29] Thus, small-airway disease plays a major role in a current disease model that might be applicable to air pollution studies.

Some persons with COPD also have airway hyperreactivity and bronchospasm; many of these are long-term asthmatics who have developed a degree of fixed airway obstruction.

These components can exist alone or in any combination. Widespread use of the term COPD came about because it is difficult for clinicians to separate the roles of the separate components in individual patients or in populations. Some persons have evidence of considerable irreversible damage to lung tissue before breathlessness, the cardinal symptom of COPD, appears.

In view of these difficulties, COPD is defined operationally, rather than pathologically. A common definition is that COPD is present when FEV_1 is less than 65% of the predicted value and the FEV_1:FVC ratio is less than 80% of predicted[68] when predicted values are based on age, sex, race, and height. Hence, COPD may be considered synonymous with chronic airflow limitation. The selection of airflow limitation as the defining feature of the syndrome also appears to be the appropriate public health definition, because the loss of expiratory airflow is a better predictor of long-term survival than the presence of coughing and sputum production. Survival and morbidity are heavily influenced by the susceptibility of persons with COPD to respiratory infections, such as influenza, and those infections are likely to be more serious in them than in persons with normal lung function.

Much has been learned about the components of COPD since the early 1950s, when chronic bronchitis was recognized clinically, but not considered important. Diagnosis of emphysema was difficult and considered unimportant, because it could not be treated. Pulmonary function tests were used in only a few centers, and FEV_1 had not been studied in detail.

The ease of carrying out pulmonary function tests and the use of FEV_1 as an indicator of COPD progression led to the relatively rapid definition of etiologic factors in COPD. Established etiologic factors are cigarette smoking; some occupational exposures, such as to coal, cotton dust, and toluene diisocyanate; advanced age; high concentrations of SO_2 and particles; and genetic factors, such as deficiency of α_1-antiprotease, which occurs in a very small percentage of the population and increases susceptibility to emphysema. Some evidence supports a history of respiratory infection in childhood as another risk factor.[144] Higgins and co-workers have developed useful models for predicting chronic airflow limitation on the basis of age, sex, smoking history, and initial FEV_1.[78]

The hypothesis that current air pollution is important in the etiology of COPD is plausible, but has not been adequately assessed. Few of the available studies could examine overt clinical disease or separate recent from long-past, heavier exposures. Furthermore, the design of some studies did not permit a distinction between an aggravating effect on existing disease and an etiologic effect. Chronic coughing and sputum production are commoner in areas with greater SO_2 and particulate pollution than in less polluted areas,[43] and some data suggest that increased oxidant pollution is associated with an increase in chronic wheezing.[33] There is also inconclusive evidence of an increased occurrence of severe emphysema in more polluted cities.[157] A recent study in several French cities found a higher prevalence of chronic respiratory symptoms in areas of greater SO_2 pollution.[68]

Various lines of evidence from animal studies support the view that exposure to less severe air pollution can cause chronic lung disease. Researchers who have induced destruction of alveolar walls, the primary lesion in emphysema, by instilling proteolytic enzymes intratracheally have produced nearly identical lesions with long-term exposure to NO_2 or O_3.[139] Chronic exposure to SO_2 at very high concentrations (400-600 ppm) produces chronic bronchitis in rats and dogs,[59 85] but the relation of this finding to human disease at ambient SO_2 concentrations (the National Ambient Air Quality Standard is 0.03 ppm over a year) is unknown.

Changes in Rate of Lung Function Growth and Decline

Lung function normally develops at a predictable rate, reaching a plateau in the late teens and then decreasing at a relatively constant rate from the twenties onward.[18 86] Various types of diseases result in deviations from this healthy function curve. Although an increase in the rate of loss of pulmonary function might indicate accelerated aging, its chief use is as an indicator of the risk of COPD. Similarly, the effects of retarded lung growth are not known, but young adults who achieve lower peaks of function presumably will have less reserve to resist the development of COPD. Lower rates of increase in lung function are not synonymous with retardation of lung growth, but the terms are sometimes used interchangeably because lung function is the only readily measurable indicator of the growth process. Recent analyses from the Harvard Air Pollution Health Study indicate that increased exposure to some indoor air pollutants contributes to slower lung development in children between the ages of 6 and 12.[154]

For white males about 1.7 meters tall, normal FEV_1 is approximately 4,400 ml at the age of 25 and slowly declines to about 2,900 ml by the age of 70.[161] Disability normally occurs when FEV_1 is about 30% of the value expected at age 25.[44] Smokers experience more rapid declines than nonsmokers. If smoking stops, the rate of decline becomes similar to that of nonsmokers, but the lost function is not recovered.

An effect of pollution on the rate of decrease in FEV_1, and thus presumably on the risk of COPD, can be inferred from cross-sectional data from Britain[73] and, more recently, from France.[60] In the latter study, average FEV_1 in men was 3,600 ml in areas with SO_2 concentrations averaging 10 $\mu g/m^3$ and 3,400 ml in areas with SO_2 averaging 100 $\mu g/m^3$. A recent study of women who were long-term residents of an area of Los Angeles characterized by persistent photochemical oxidant pollution found a variety of chronic pulmonary function deficits after adjustment for smoking.[84] A longitudinal study from the Netherlands found a faster decrease in FEV_1 in a population near Rotterdam than in a rural population.[168] Finally, on the basis of another longitudinal study, R. Detels *et al*. (unpublished manuscript) reported that current concentrations of air pollutants in Los Angeles are associated with measurable differences in the rate of change of some sensitive indexes of lung function.

Summary

Several factors make it particularly difficult to study the relationship of air pollution and chronic respiratory disease. Although the components of COPD can be more easily distinguished now than in the early 1950s, they still occur together often. Physicians often do not distinguish which components are present. And some causes of COPD, especially smoking, are more likely than ambient air pollution. The extent to which specific air pollutants interact with other factors, including smoking, to contribute to the various components of COPD or to abnormal rates of change of lung function has not yet been determined.

Gaps in understanding of the natural history of lung diseases, especially COPD, constrain our ability to study the role of air pollution in causing them. We would like to know the relationship of long-term lung function to transient changes in lung function, to the presence of such symptoms as wheezing and coughing, to airway hyperreactivity (particularly because persons with hyperreactive airways generally have lower respiratory function than do normal persons), to respiratory infections in childhood, and to lower rates of lung growth in childhood. Why some smokers develop rapid deterioration in lung function while others with similar smoking patterns do not is a question of some relevance to air pollution epidemiology. The relationship of small-airway disease to COPD is also of great interest, in that small-airway disease can be an early lesion of pollution-induced COPD, as well as of smoking-induced COPD. Answers to these and related questions will have a critical effect on the development of better hypotheses and better methods for epidemiologic studies of air pollution, as well as on the definition of susceptible populations and the selection of appropriate measures of adverse health effects.

LUNG CANCER

Lung cancer is the most common form of malignancy among men in the United States, and it is becoming the most common among American women. In 1983, lung cancer caused approximately 120,000 deaths in the United States.[165] Although operative mortality and the treatment of localized lung cancer appear to have improved slightly in recent years, the overall 5-year survival rate for lung cancer is still only 13%.[148] The number of deaths caused by lung cancer must be reduced through prevention.

Lung cancer has multifactorial origins and can result from interaction among several causal agents. Tobacco smoking is clearly the most important, followed by some occupational exposures.[35] Passive smoking[83] and indoor air pollutants (particularly radon gas and its decay products[8]) have also been strongly suggested to cause lung cancer.

The proportion of lung cancers due to each of these factors is difficult to ascertain. Factors other than smoking account for smaller and more variable fractions of lung cancer than does smoking, and they sometimes seem to exert their effects interactively with smoking or other factors. For example, lung cancer occurs 5 times more commonly among nonsmoking asbestos workers than in the general population, but 53 times more commonly among smoking asbestos workers than in the general population.[63] It occurs 6 times more commonly among nonsmoking underground uranium miners exposed to radon than in the general population, but 10 times more commonly among smoking miners than in the general population.[170] Laboratory rats that failed to develop bronchogenic carcinomas after inhaling the known chemical carcinogen benzo[a]pyrene alone developed this malignancy after inhaling the carcinogen plus SO_2.[93]

A paradoxical consequence of these multiple interactions is that any attempt to add the proportions of lung cancer cases attributable to each separate factor will tend to produce a total greater than 100%. A particular case of lung cancer, such as a case in a smoking asbestos worker who resided in a heavily polluted neighborhood, could legitimately be attributed to as many as three causal factors (and might have been prevented if exposure to any of them had been reduced). Thus, simple addition and subtraction to determine the proportions of lung cancer attributable to various causal factors will not suffice. Perhaps for that reason, published estimates of the fraction of lung cancer attributed to ambient air pollution have varied widely.[35 83]

Despite these uncertainties about the magnitude of the effect, several lines of evidence support the hypothesis that ambient air pollution contributes to the etiology of lung cancer.[35 83 93 153]

- *Chemical analyses* show carcinogens in polluted urban air, including polycyclic aromatic hydrocarbons (such as benzo[a]pyrene), asbestos, and arsenic.[35 61 63 97 103 152]

- *Toxicologic studies* have shown that extracts of materials from polluted ambient air can cause tumors, including lung tumors, in mice, rats, and hamsters; chromosomal damage; and injury to DNA.[128]

- *Epidemiologic studies*--including geographic studies,[45 58 67 128 171] studies of the urban-rural gradient,[54 67 153] point-source studies,[19,20,108,120,135,147] studies of time trends,[12,67] and migrant studies[37,142]--have often suggested an association between lung cancer and air pollution.

Nearly all these epidemiologic studies failed to collect information from individual members of study populations on such important, potentially confounding factors as age, social class, tobacco smoking, and occupational exposures.[153] Furthermore, statistical adjustment for differences in demographic features or for aggregate tobacco consumption generally reduces the size of the reported associations.[54,67,153] Those issues have been particularly carefully assessed with regard to the "urban factor" (observed urban-rural gradient).[54,67]

In summary, it is plausible that ambient air pollution causes some part of the lung cancer incidence in the United States, but the size of the fraction is still not known.[83,153]

NONRESPIRATORY END POINTS

Although the Committee has elected to focus on respiratory end points, air pollution is either known or thought to be a causal factor in other major health problems, and epidemiologic studies will be necessary if these problems are pursued. These problems generate methodologic questions that are quite different from those emphasized in the remainder of the report.

Lead, Neurobehavioral Effects in Children, and Essential Hypertension

Lead is ubiquitous in the modern environment.[122] It is found in air, soil, water, dust, and food. Current environmental concentrations of lead are several thousand times higher than those of the prehistoric era.[121] Lead can be absorbed by inhalation or ingestion. Inhalation is the more efficient of the two. The dose-response relationship between air lead and blood lead has been evaluated extensively. In adults without prior exposure to lead, each 1-$\mu g/m^3$ increase in ambient air lead content appears to increase the blood content by approximately 1 $\mu g/dL$. In children, each 1-$\mu g/m^3$

increase in ambient air lead content causes a mean increase in blood lead content of 2 μg/dL or more.[92]

A major source of environmental lead in the last 50 years has been the release into the atmosphere of several hundred thousand tons of lead particles each year from the combustion of leaded gasoline.[122] Ambient concentrations of airborne lead vary widely.[162] Immediately adjacent to primary lead smelters in the United States, annual mean air lead concentrations as high as 93 $\mu g/m^3$ have been recorded.[92] Concentrations elsewhere are lower; because they are affected principally by the combustion of leaded gasoline, these concentrations correlate with the density of motor-vehicle traffic.[80] Air lead concentrations in the United States have decreased substantially,[5] beginning in the mid-1970s and in parallel with the reduction in lead content of American gasoline.[5 17]

A major subject of study in recent years has been whether ambient lead at current concentrations causes subtle neurologic toxicity in apparently asymptomatic persons. Several carefully controlled studies have shown decrements in IQ of 3-7 points in asymptomatic children with modestly increased lead burdens. These decrements remained after socioeconomic status, perinatal history, child-rearing practices, and other sociologic variables were accounted for in the analyses.[123 124 149 160]

In a recent review of these epidemiologic studies, Yule and Rutter considered it "highly implausible" that the consistent differences in IQ score could have arisen by chance[176] and estimated that the exposure of children to lead in ordinary modern urban environments causes a mean decrement in IQ score of 2-5 points. Needleman et al. have noted that a 4.5-point shift in mean IQ score is associated with a tripling in the number of children with IQ scores below 80 and with a significant reduction in the number with superior IQ scores (above 125).[124]

Data from the second National Health and Nutrition Examination Survey (NHANES II) indicate that 3.9% of American children (18.6% of urban poor black children) between the ages of 6 months and 5 years examined in 1976-1980 had blood lead concentrations of 30 μg/dL or more,[4] the concentrations considered indicative of increased lead absorption. From those data, it can be estimated that 675,000 young children have high blood concentrations. The Centers for Disease Control recently revised the definition of increased lead absorption in children from 30 μg/dL to 25 μg/dL; a substantially larger number of children would be classified as having high blood lead according to that new definition.[160]

The findings of NHANES II suggest that subtle, but irreversible, lead encephalopathy might be widespread among young American children. Although the NHANES II data show that children's blood lead decreased between 1976 and 1980, in parallel with reductions in the consumption of leaded gasoline,[5] the Committee believes that the potential magnitude of the neurobehavioral problem warrants further epidemiologic study.

Lead has long been recognized as toxic to the kidney.[57] Prolonged high-dose exposure to lead both in children[40] and in adults[57] has been shown to produce nephropathy, which can lead to secondary hypertension. Hypertension, although not a constant finding, has been reported in association with occupational lead exposure[30,34,41] in the absence of severe renal disease. A recent epidemiologic study based on data collected in NHANES II found that blood lead in American men aged 40-59 was significantly associated with increases in systolic and diastolic blood pressure.[64,138] These findings are supported by low-dose feeding experiments in animals and warrant further epidemiologic study.

Benzene and Leukemia

Ambient air contains small amounts of many volatile organic chemicals that are known or suspected carcinogens. The data base for estimating the health effects of these exposures is far more extensive for benzene than for other substances.

Epidemiologic studies of rubber workers[78,143] and chemical workers[130] have shown that benzene causes leukemia. These results have been corroborated by carcinogenesis bioassays[106,107,150] and by studies of chromosomal damage in persons exposed to benzene.[137] Recent epidemiologic risk assessments have suggested that the risk of death from leukemia is increased in industrial workers with mean annual exposure to benzene below 1 ppm (equivalent to 3,190 $\mu g/m^3$) over a 40-year working lifetime.[79,143] Benzene concentrations in ambient air in the United States range from 0 to 22 $\mu g/m^3$ (annual arithmetic mean values), and quarterly means as high as 400 $\mu g/m^3$ have been noted.[76] Benzene at ambient concentrations has not been demonstrated to cause leukemia or other cancers, nor is it likely that such an association could ever be directly demonstrated by epidemiologic study, given the generally low exposures, the almost total lack of information on past exposures, and the poor definition of confounding variables that are typical of community populations.

Carbon Monoxide and Ischemic Heart Disease

Tissue hypoxia is the principal toxic effect of carbon monoxide, CO.[62] Inhaled CO binds tightly to circulating hemoglobin, producing carboxyhemoglobin, COHb, and thus reducing the ability of the blood to transport oxygen.[113,159] The heart and brain are the organs most severely affected by CO. Extensive evidence links low-concentration CO exposure to altered hemodynamics. In normal exercising adults, venous oxygen tension is decreased during exposure to CO, and heart rate, cardiac output, and coronary arterial blood flow are all increased.[9,169]

In persons with coronary arterial disease, a compensatory increase in coronary blood flow does not occur after exposure to CO,[9] so such persons are at heightened risk of CO toxicity. Exercising subjects who have coronary disease develop angina and electrocardiographic abnormalities more rapidly when breathing air containing CO at 50 or 100 ppm than when breathing air without CO.[3] Because cigarette smoke contains high concentrations of CO,[159] similar toxic effects can be produced by smoking. In animal experiments, CO inhalation at relatively low concentrations has been associated with cardiac arrhythmias, including ventricular fibrillation.[32]

Visitors to high altitudes, fetuses and infants, and persons with peripheral vascular disease, COPD, or anemia also seem to be at heightened risk of CO toxicity.[159]

COHb concentration is an excellent example of a short-term biologic marker of exposure that can be a valuable tool in clinical and epidemiologic studies. NHANES II found that the national mean COHb concentration in nonsmokers in the United States was 0.77%, compared with 4.2% in smokers.[141] The NHANES data also showed higher COHb concentrations in cities than in rural areas. This gradient was evident in children and in adults who had never smoked, as well as in smokers. The gradient was steeper in blacks than in whites, perhaps owing to heavier occupational exposure of blacks or residential proximity to traffic. Concentrations were higher in winter than in summer.

Epidemiologic studies of cardiovascular disease in relation to ambient CO concentrations have so far been inconclusive. A study in Los Angeles[28] found higher case-fatality rates for myocardial infarction in areas of "high" air pollution than in comparison areas, and the difference was observed only during periods of increased CO pollution. Weekly ambient CO concentrations were low, ranging from 5.1 to 14.0 ppm. However, a study in Baltimore found no correlation between CO exposure and sudden death from acute myocardial infarction.[91]

Volatile Organic Chemicals and Neurotoxicity

Chronic exposure of industrial workers, such as painters, to volatile organic solvents is associated with a subtle and irreversible syndrome of chronic encephalopathy.[7] [98] [146] The data are insufficient to determine whether exposure to volatile organic chemicals in the general environment is associated with chronic neurotoxicity. It appears prudent to define and measure the syndrome of solvent-induced encephalopathy in industrial workers with heavy exposures before trying to assess possible solvent-induced encephalopathies in the general population. Exceptions might be made for heavily exposed populations, such as persons living near point sources of emission. Priority in future evaluations should be given to the development of methods for improved assessment of exposure and improved quantitation of toxic neurologic effects.[10]

SOURCES OF HEALTH EFFECT DATA

Many kinds of data can be used to determine health status in an epidemiologic study. Most of the data sources to be discussed in this report are specific to the respiratory effects discussed earlier, although some have broader applications. The different methods of obtaining data have different advantages and disadvantages with important implications for the design and ultimate sensitivity of a given study. Data come from a wide variety of sources, including clinical records, vital statistics, population-based surveys, data bases established for other reasons, and special inquiries. In many epidemiologic studies on air pollution, different kinds of data from different sources are used together.

QUESTIONNAIRES

The questionnaire is a common tool for measuring indicators of respiratory disease, especially chronic disease. It can be used either alone or (preferably) in conjunction with more objective measures. Like other instruments, questionnaires need to be standardized and calibrated to ensure that they measure the desired end points. Quality control of questionnaire data has been studied extensively.[65]

In 1960, the British Medical Research Council approved a standardized questionnaire to assess respiratory health, particularly chronic conditions.[115] It has undergone several revisions, and the most recent (ATS-DLD-1978) was designed specifically to yield reproducible results, whether it is filled out by the subject without assistance or jointly with an interviewer. Detailed explanations of the testing procedures and the validity and reliability of items in the questionnaire are available in the literature.[42] The revised version includes several items on asthma and pediatric respiratory diseases. Particular research applications might require the flexibility to alter some questions or to include more specific questions on some topics, such as occupational exposures. Although prospective studies on such end points as exacerbations of bronchitis, emphysema, and asthma often use daily or weekly diaries, such diaries have not been standardized. On balance, the continuing development of standardized questionnaires is valuable to epidemiologists, not only because it improves the utility of questionnaire data, but because it facilitates comparisons among different studies.

Questionnaires have recognized limitations that have been summarized in review articles and need further methodologic research.[96] One common problem is recall bias: sick people are more likely to recall possibly associated factors than healthy people, and exposed people are more likely to recall illness than nonexposed people. Thus, cancer patients might report their industrial exposures, or smokers their respiratory symptoms, more completely than well persons or nonsmokers. The reliability (reproducibility) of questionnaire responses of persons with chronic lung disease is also a matter of concern.[136] Gandevia has recently discussed several innovative approaches to quantifying respiratory symptoms in epidemiologic studies of environmental inhalants.[47]

PULMONARY FUNCTION TESTING

Pulmonary function tests of the mechanical aspects of airflow (spirometry) are noninvasive, quick, reproducible, sensitive, specific, and easy to perform in the field. These characteristics, in contrast with those of tests of renal or cardiac function, for example, have made it feasible to use respiratory function as an end point in epidemiologic studies and to define exposures and risk factors associated with deficits in pulmonary function. Although spirometry is the most commonly used technique, others are being developed and offer some promise of epidemiologic utility. The newer techniques generally measure quantities other than airflow. They include bronchial hyperreactivity testing, tests for particle deposition, and magnetopneumography to measure macrophage function and dust clearance.

The use of a spirometer to analyze a single forced expiration is one of the most valuable techniques in the armamentarium of pulmonary function researchers. The subject inhales fully and then exhales as hard and as fast as possible into a mouthpiece. Test results are subject to many sources of variation, especially in large longitudinal studies that involve many instruments, technicians and sites.[2 15 16 25 31 49-51 75 140 177] All the instruments require extensive testing and calibration. Well-trained technicians, appropriate instructions to the subjects, and careful evaluation of the tests are also needed. A subject learns by performing the test, so the first measurement is usually lower than later ones. Problems in interpreting longitudinal data can arise from regression to the mean, extraneous exposure factors at some but not all test sessions, incomplete understanding of the normal curves for lung growth and decay, biologic variability among subjects, and lack of agreement as to the best methods of statistical analysis.

The most useful spirometric measurement is FEV_1, which is the maximal amount of air that the subject can exhale in 1 second. The peak expiratory flow rate, measures of flow at various lung volumes, and forced vital capacity are also used often. When carried out properly, spirometric tests are extremely sensitive. Thus, Ware et al. detected changes in FEV_1 of less than 1%, or 10-20 ml of a total of about 2,000 ml, when they compared children of smoking and nonsmoking parents.[172] Subjects with FEV_1 values that vary excessively during a single test session are often discarded from studies, yet it was recently reported that such persons have more rapid decline in function over time than those who give repeat efforts within recommended limits.[39] These kinds of problems are now receiving increasing attention.

Several other measurements based on forced expiratory flow are more difficult to use than FEV_1, but yield valuable information. These measurements, such as mid-expiratory flow rates, are more sensitive for some effects than FEV_1, but are subject to wider normal variation, including a greater measurement error. Measurements of gas diffusion (diffusing capacity) in the lung with a portable single-breath device have recently been used in occupational survey work and are being applied in air pollution epidemiology.[84] The development of portable peak flow meters that the subject can use to record repeated measurements might present opportunities for more extensive studies of respiratory function under varying conditions.

FEV_1 is related primarily to the function of the large airways. By the time large-airway effects are detectable, changes have usually occurred in the smaller airways. Researchers are therefore trying to devise simple tests that measure effects in small airways and can be used in the field. One measure of small airway function involves the single-breath nitrogen test, in which the subject takes one breath of pure oxygen and then the distribution of nitrogen exhaled in the next breath is determined. In a normal lung, the percent of nitrogen is relatively constant during most of the breath; if small-airway disease is present, the percent of nitrogen increases substantially during the end of the breath. Lippmann and co-workers have been adapting, for field use, a sensitive laboratory technique to measure the dispersion of a nontoxic aerosol in exhaled air as an index of the overall distribution of ventilation in remote areas of the lung.[110]

Airways are tested for reactivity by having the subject inhale a substance, such as methacholine or cold air, that induces airway narrowing. People vary greatly in the amount of material needed to induce a specific decrease in spirometric measures.[24, 26] Hyperreactivity testing is now an epidemiologic tool, inasmuch as rapid and convenient techniques have become available in the last 4 years and have been applied to populations in the field.[174]

The ability of the lungs to clear dust and other small particles is another measurable lung function. This characteristic is receiving increased attention, because inhaled dust and smoke can cause or aggravate lung disease by damaging clearance mechanisms. Short-term clearance can be measured with safe, rapidly decaying radioactive materials, but long-term clearance is more difficult to measure.

One promising laboratory technique for studying dust clearance requires that the subject inhale nontoxic magnetic particles. The location and clearance of these particles are then followed over a period of months. In one such experiment, approximately 50% of the dust remained in the lungs of three smokers after 11 months, whereas only about 10% remained in the lungs of nine nonsmokers.[27] Further research is needed to reduce the cost of this technique and to explore the relationship of clearance to deficits in other pulmonary functions.

MORBIDITY AND MORTALITY RECORDS

Death certificates are the standard source of mortality data, but sources and types of routinely collected morbidity data are varied. They include such end points as hospital admissions, visits to emergency rooms, numbers of days lost from work or school, and numbers of visits to physicians.

Whatever methods are used to determine morbidity and mortality for an epidemiologic study, determinations of health end points are subject to many errors in diagnosis, reporting, coding, and recordkeeping. In addition, hospitals and physicians vary within the acceptable range of practice. If a study extends over many years, techniques of diagnosing and treating diseases can change, as can definitions of diseases. In respiratory diseases, there is an increasing trend toward use of "COPD," rather than the more specific "emphysema" or "chronic bronchitis," in hospital records and on death certificates; this is due in part to the decreasing rate of autopsy. Thus, apparent trends or geographic differences in COPD mortality might reflect changes in terminology or diagnostic practices. Even if the reliability of morbidity data were to remain the same, availability of such data on entire, defined populations would constitute a major advance for air pollution epidemiology. The epidemiologic approach, comparing disease rates in large groups, can sometimes use diagnostic data whose validity on an individual basis is lower than the standard of validity required for clinical medicine.

The appearance of health care financing based on diagnosis-related groups (DRGs) will increase the availability of population-based data on hospitalization, although detail might be seriously limited and biases substantial. The National Center for Health Statistics conducts various population-based surveys of morbidity, such as the [illegible]tional Health Interview Survey and the National Ambulatory Care Survey (in which physicians report on various demographic characteristics and medical problems of office patients); the use of these surveys is discussed in Chapter 4. Centralized population-based registries of specific diseases are another source of information. The National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program has improved understanding of both cancer incidence and cancer mortality.[163]

Several difficulties impede the linkage of routinely collected morbidity data to potential causal factors, such as air pollution. The role of social and economic factors in determining the likelihood that a person with a given illness will seek health care is not yet well understood and could cause substantial bias in routinely collected morbidity data. Without population-based health services, it is not easy to link separate health records on a person so that the researcher will have complete information. Record-linkage studies also require a high degree of sensitivity to concerns about privacy and confidentiality.

Death certificates are a crucial part of many epidemiologic studies. With the development of the National Death Index, researchers can now ascertain the fact and location of death from a central repository before requesting death certificates from individual states.[166] Although mortality data are most useful for studies of lung cancer, they do provide a few important opportunities for studying the relationship of air pollution to other respiratory diseases when large data sets are available. The extent and nature of these opportunities have not been fully explored.

Death certificates are not always a source of accurate information about cause of death, particularly for diseases that are difficult to diagnose or code.[133] Autopsies are the surest mechanism for confirming whether the cause of death on a certificate is correct, but the overall rate of autopsies has been decreasing and was only approximately 14% in this country in 1982.[164]

BIOLOGIC MARKERS OF RESPIRATORY EFFECTS

Biologic markers can be categorized as exposure markers, effect markers, or susceptibility markers. Exposure markers indicate that exposure to a substance of concern has occurred and sometimes allow estimation of absorbed dose and dose to target tissues. Effect markers show early results of interaction between substances of concern and cellular or molecular targets in the host. Susceptibility markers indicate that some characteristic of the host, independent of the exposure, increases the chance that disease will occur; an enzyme deficiency is an example. Whether a marker is considered an effect marker or an exposure marker can depend on how a researcher uses the information in a particular study. This discussion primarily concerns effect and susceptibility markers.

Future studies are likely to make increasing use of subclinical data, including effect markers, for several reasons. First, current ambient air pollution in the United States is unlikely to produce statistically significant changes in clinical outcomes unless very large numbers of persons are studied; early markers of disease will constitute surrogate end points that generally will be more common than the ultimate disease and thus will allow detection of relationships with fewer subjects. Second, early markers can be detected sooner than clinical effects and so reduce the time needed for observing populations in followup studies. Third, the use of sensitive indicators might improve researchers' ability to classify individual subjects correctly as affected or unaffected. Finally, research on detecting adverse effects of air pollution at an early subclinical stage has the potential to provide clinicians with opportunities to prevent clinical disease.

Further development is needed before biologic markers are ready for routine use in epidemiologic studies of air pollution. Their accuracy in measuring what they are intended to measure, their value in predicting health impairment or premature death, and their applicability to various demographic groups are not yet fully established. Regardless of the extent to which markers fulfill their promise, clinical data will continue to be used in air pollution epidemiology.

To be useful in epidemiologic research, markers must be validated. The procedures and techniques used to measure a marker must generally be noninvasive, precise, sensitive, specific, easy to use, and inexpensive. Although biologic markers are commonly used in clinical research and in epidemiologic studies of infectious diseases, they have seldom been used for studying pulmonary effects. One reason is that spirometry has been extraordinarily useful in measuring pulmonary function. Second, the complex cellular and biochemical processes of the lung, the heterogeneity of cell types, and the changes that occur in disease have only recently begun to be understood. Third, lung tissue and fluids are not easily obtained noninvasively--an important factor when large and relatively healthy groups are under study.

Urine, blood, sputum, saliva, and nasal mucosa are readily accessible for noninvasive detection of functional, biochemical, or structural changes in the respiratory system. Bronchoalveolar lavage (BAL) is a major advance for clinical and toxicologic research, but it is not appropriate for most large-scale epidemiologic studies, because it is invasive and expensive. It is possible, however, that pathology specimens of cells or tissue from BAL, biopsies, or even autopsy could be used in special types of epidemiologic studies. Specimens from patients without interfering disease can be selected (for instance, from a tissue bank) and retrospective exposure histories obtained. For example, studies examining alveolar inventory and fine structure in populations free of clinical lung disease (e.g., coroner's cases) are feasible.

Specimens from Sputum and Nasal Mucosa

Sputum cytology has been used in studying nonneoplastic bronchopulmonary disorders.[125] Nobutomo compared the sputum cytology of nonsmoking residents of two towns, one of which had sulfur oxide (SO_x) and particle concentrations several times higher than the other.[129] Increased numbers of inflammatory cells were found in sputum of residents of the more polluted town, and these findings preceded development of such signs of respiratory disease as increased phlegm. Investigators from Norway recently reported standardization of a new technique for counting expectorated alveolar macrophages in workers exposed to dust and gaseous irritants.[127] Further development of the method might permit more convenient evaluation of this important effector cell, which is believed to have a fundamental role in several pathogenic processes in the lung. Biochemical tests on sputum, such as measurement of antiproteases, might also provide important leads. For example, sensitive enzyme-linked immunoassays on sputum have identified a low-molecular-weight antiprotease (bronchial protease inhibitor) that is active in the bronchial areas of the lung.[88]

Use of sputum for studying COPD and other respiratory diseases warrants further research. Problems in the use of sputum samples in population studies include difficulties in standardizing the methods for obtaining reliable samples, particularly from healthy subjects, and in interpreting findings, in that cells and other substances found in sputum reflect not only secretions from both upper and lower respiratory tracts, but also materials from the mouth.

Some important biochemical and cellular features of nasal mucosa can also be investigated with nasal brushing, a new noninvasive technique.[104] This technique might be useful in epidemiologic research, because the nasal mucosa is vulnerable to the effects of pollutants and can reflect damage to more critical areas in the lower respiratory tract. For example, it has been shown that ciliary beat frequency can be measured with a simple photoelectric device and that results obtained on samples from nasal mucosa are highly correlated with results from bronchoscopy.[104] A recent study has shown that repeated nasal-brush sampling (even in children) is feasible and can be used to describe the evolution of changes in ciliary morphology before, during, and after acute viral infection or short-term exposure to O_3.[21] [22]

Blood and Urine Markers for COPD

A task force of the National Institute of Environmental Health Sciences[167] recently reported on investigations to determine early markers of COPD. The task force concentrated on emphysema, because recent breakthroughs in understanding its biochemical basis might permit the development of several markers for use in clinical research and epidemiology. The disease involves changes in the alveolar walls, and research has focused on changes in the elastin and collagen that make up these walls. Researchers now believe that the connective tissue matrix of the alveolar wall in the healthy lung is protected from destruction by a balance of protease and antiprotease. In the development of emphysema, however, a net excess of proteolytic activity leads to destruction of the matrix. Measurable elements (reactants or products) in the protease-antiprotease balance could be valuable markers.

Various environmental factors, including cigarette smoking and exposure to oxidants, increase the release of protease and endogenous oxidants from neutrophils and macrophages and decrease antiprotease activity. Protease concentrations and activity can be measured in bronchoalveolar lavage fluid, but these measurements have not yet been extended to blood or urine. Antiprotease can be measured in blood, since the landmark discovery of α_1-antiprotease deficiency by Laurell and Eriksson in 1963.[95] Persons with this genetic deficiency are especially susceptible to emphysema,[46] but variations in total serum antiprotease among normal persons and persons who are heterozygous for the enzyme do not seem to reveal much about the risk of emphysema.

α_1-Antiprotease, the major antiprotease in humans, is damaged in a highly specific way by endogenous or exogenous oxidants.[81] The damage involves cleavage of the protein backbone at a specific methionine-serine linkage in the molecule. The recent development of extremely sensitive assays for the detection of damaged antiprotease fragments has opened the possibility of their use as markers of exposure or effect.[158]

Among the various proteases, elastases might be critical in the pathogenesis of emphysema. Elastase has been assessed by measuring elastin fragments in serum with the use of antibodies to the various peptide fragments.[114] Elastin-derived peptides were detected in the serum of dogs that had been exposed to an elastase-containing aerosol to induce emphysema-like lesions. More recent clinical research has suggested that serum concentrations of these peptides are distinctly different between people with COPD and normal people and between heavy smokers without disease and nonsmokers.[89] Assays for these fragments in urine have not yet been as successful.[132] Detection of elastin fragments in serum might therefore provide the basis of an early biologic marker for emphysema that could be tested soon.

Recent advances in understanding the role of factors measurable in plasma, such as ceruloplasmin and catalases, which protect the lung from injury by oxidants and free radicals, might lead to other markers of susceptibility that could be used in epidemiologic studies. Ceruloplasmin, for instance, "is the major antioxidant of plasma" and might be a particularly important determinant of lung defense in persons chronically exposed to oxidants.[155]

Studies of other rare genetic diseases of connective tissue in humans and animals could increase our understanding of COPD etiologies and the identification of markers relevant to the disease. Examples include Marfan's syndrome and lysyl oxidase deficiency, a genetic disease that specifically decreases the cross-linking of collagen fibers.

Changes in lung collagen have also been proposed as markers of chronic pulmonary disease. Collagen constitutes 6-20% of the dry weight of the lung, and elastin 3-5%. The ratio and distribution of distinct types of collagen vary as a consequence of several disease states, and chronic lung disease induced in animals by long-term O_3 exposure is associated with an increase in total lung collagen content.[94] The specific collagens can be detected with immunochemical procedures.[11] Furthermore, Michaeli and Fudenberg found that 70% of patients with emphysema had antibodies to denatured collagen in their serum, compared with 9% of control subjects.[117] Antibody titers were also higher for the emphysema subjects.

The amino acid hydroxyproline might also serve as an indicator of the status of lung connective tissue. Hydroxyproline is found almost exclusively in collagen, and lung collagen has a higher ratio of hydroxyproline to proline than does collagen in other tissues.[90] Studies in guinea pigs have indicated that long-term exposure to NO_2 increases the urinary excretion of hydroxyproline.[87] Matsuki and colleagues have measured the ratio of hydroxyproline to creatinine in urine in several types of human subjects, including smokers and COPD patients.[109 175] In the only epidemiologic studies to use this marker so far, they found increases in urinary hydroxyproline with increased exposure to NO_2 and with passive smoking (in children).[109] Although these results are of great interest, more fundamental research is needed to identify the determinants of intra-individual and interindividual variation in hydroxyproline excretion and to understand the clinical meaning of observed changes.

Markers of Genetic Toxicity

Carcinogenesis is a multistep process, and years are presumed to intervene between the early steps and eventual disease manifestation. If researchers could detect early stages of the disease process, followup studies of groups would be more feasible, and further exposure might be preventable. Many carcinogens cause mutations or other genetic damage, and researchers have developed several tests for possible markers of cancer risk.[134] Such tests would be applied in two ways in air pollution epidemiology: to determine degree of exposure, and to identify persons especially sensitive to genetic damage by particular agents. The relative importance of exposure and susceptibility can be influential in interpreting results. The use of these assays as indicators of exposure is discussed in Chapter 3.

Genetic toxicity is detectable soon after exposure, so the option of taking steps to prevent further exposure or to continue monitoring might be available. Genotoxicity tests have been used in various occupational settings and among populations known to be exposed to low concentrations of toxic environmental chemicals, such as ethylene oxide and benzene. Future studies are needed to clarify further the relationship of these end points to development of disease.

REFERENCES

1. American Thoracic Society. Guidelines as to what constitutes an adverse respiratory health effect, with special reference to epidemiologic studies of air pollution. Am. Rev. Respir. Dis. 131:666-668, 1985.

2. American Thoracic Society. Respiratory care position paper. ATS News 4(6), 1976.

3. Anderson, E.W., R.J. Andelman, J.M. Strauch, N.J. Fortuin, and J.H. Knelson. Effects of low-level carbon monoxide exposure on onset and duration of angina pectoris: A study in ten patients with ischemic heart disease. Ann. Int. Med. 79:46-50, 1973.

4. Annest, J.L., and K.R. Mahaffey. Blood Lead Levels for Persons 6 Months-74 Years, United States, 1976-1980. Vital and Health Statistics, Series 11, No. 233. DHHS Publication No. (PHS) 84-1683. Hyattsville, Md.: National Center for Health Statistics, 1981. 61pp.

5. Annest, J.L., J.L. Pirkle, D. Makuc, J.W. Neese, D.D. Bayse, and M.G. Kovar. Chronological trend in blood lead levels between 1976 and 1980. N. Engl. J. Med. 308:1373-1377, 1983.

6. Avol, E.L., W.S. Linn, T.G. Venet, D.A. Shamoo, and J.D. Hackney. Comparative respiratory effects of ozone and ambient oxidant pollution exposure during heavy exercise. J. Air Pollut. Control Assoc. 34:804-809, 1984.

7. Axelson, O., M. Hane, and C. Hogstedt. A case-referent study on neuropsychiatric disorders among workers exposed to solvents. Scand. J. Work Environ. Health 2:14-20, 1976.

8. Axelson, O., and L. Sundell. Mining, lung cancer and smoking. Scand. J. Work Environ. Health 4:46-52, 1978.

9. Ayres, S.M., S. Gainelli, Jr., and H. Mueller. Myocardial and sytematic responses to carboxyhemoglobin. Ann. N.Y. Acad. Sci. 174:268-293, 1970.

10. Baker, E.L., Jr., R.G. Feldman, R.F. White, J.P. Harley, G.E. Dinse, and C.S. Berkey. Monitoring neurotoxins in industry: Development of a neurobehavioral test battery. J. Occup. Med. 25:125-130, 1983.

11. Bateman, E.D., M. Turner-Warwick, and B.C. Adelmann-Grill. Immunohistochemical study of collagen types in human foetal lung and fibrotic lung disease. Thorax 36:645-653, 1981.

12. Bates, D.V., G.M. Bell, C.D. Burnham, M. Hazucha, J. Mantha, L.D. Pengelly, and F. Silverman. Short-term effects of ozone on the lung. J. Appl. Physiol. 32:176-181, 1972.

13. Bates, D.V., and B. Sizto. Relationship between air pollutant levels and hospital admissions in Southern Ontario. Can. J. Pub. Health 74:117-122, 1983.

14. Bauer, M.A., M.J. Utell, P.E. Morrow, D.M. Speers, and F.R. Gibb. 0.30 ppm nitrogen dioxide inhalation potentiates exercise-induced bronchospasm in asthmatics. Am. Rev. Respir. Dis. 129:A151, 1984.

15. Becklake, M.R., and S. Permutt. Evaluation of tests of lung function for "screening" for early detection of chronic obstructive lung disease, pp. 345-387. In P.T. Macklem and S. Permutt, Eds. The Lung in the Transition between Health and Disease. New York: Marcel Dekker, Inc. 1979.

16. Berry, G. Statistical analyses, pp. 427-463. In H. Weill and M. Turner-Warwick, Eds. Occupational Lung Diseases. New York: Marcel Dekker, Inc., 1981.

17. Billick, I.H., and V.E. Gray. Lead Based Paint Poisoning Research, Review and Evaluation 1971-1977. Publication No. HUD-0000809. Washington, D.C.: U.S. Department of Housing and Urban Development, 1978. 161 pp.

18. Black, L. Early diagnosis of chronic obstructive pulmonary disease. Mayo Clin. Proc. 57:765-772, 1982.

19. Blot, W.J., and J.F. Fraumeni, Jr. Arsenic air pollution and lung cancer. Lancet 2:142-144, 1975.

20. Blot, W.J., and J.F. Fraumeni, Jr. Geographical patterns of lung cancer: Industrial correlations. Am. J. Epidemiol. 103:539-550, 1980.

21. Carson, J.L., A.M. Collier, N.G. Henshaw, C.A. Smith, and S.C. Hu. Response of human ciliated respiratory epithelium to brief in vivo ozone exposure: An ultrastructural study. Environ. Res. 37:212-227, 1985.

22. Carson, J.L., A.M. Collier, and S.C.S. Hu. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N. Engl. J. Med. 312:463-468, 1985.

23. Chan-Yeung, M., S. Lam, and S. Koener. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). Am. J. Med. 72:411-415, 1982.

24. Chatham, M., E.R. Bleeker, P. Norman, P.L. Smith, and P. Mason. A screening test for airways reactivity: An abbreviated methacholine inhalation challenge. Chest 82:15-18, 1982.

25. Clausen, J.L. Pulmonary Function Testing Guidelines and Controversies: Equipment, Methods, and Normal Values. New York: Academic Press, 1982. 368 pp.

26. Cockcroft, D.W., B.A. Berscheid, and K.Y. Murdock. Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population. Chest 83:751-754, 1983.

27. Cohen, D., S.F. Arai, and J.D. Brain. Smoking impairs long-term dust clearance from the lung. Science 204:514-517, 1979.

28. Cohen, S.I., M. Deane, and J.R. Goldsmith. Carbon monoxide and survival from myocardial infarction. Arch. Environ. Health 19:510-517, 1969.

29. Cosio, M., H. Ghezzo, J.C. Hogg, R. Corbin, M. Loveland, J. Dosman, and P.T. Macklem. The relations between structural changes in small airways and pulmonary function tests. N. Engl. J. Med. 298:1277-1281, 1978.

30. Cramer, K., and L. Dahlberg. Incidence of hypertension among lead workers: A follow-up study based on regular control over 20 years. Br. J. Ind. Med. 23:101-104, 1966.

31. Crapo, R.O., A.H. Morris, and R.M. Gardner. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am. Rev. Respir. Dis. 123:659-664, 1981.

32. DeBias, D.A. Effects of carbon monoxide inhalation on the vulnerability of the heart to induced fibrillation, pp. 119-132. In A.J. Finkel and W.C. Duel, Eds. Clinical Implications of Air Pollution Research. American Medical Association Air Pollution Medical Research Conference, December 5-6, 1974. Acton, Mass.: Publishing Sciences Group, Inc., 1976.

33. Detels, R., D.P. Tashkin, M.S. Simmons, H.E. Carmichael, Jr., J.W. Sayre, S.N. Rokaw, and A.H. Coulson. The UCLA population studies of chronic obstructive respiratory disease: 5. Agreement and disagreement of tests in identifying abnormal lung function. Chest 82:630-638, 1982.

34. Dingwall-Fordyce, I., and R.E. Lane. A follow-up study of lead workers. Br. J. Ind. Med. 20:313-315, 1963.

35. Doll R., and R. Peto. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J. Nat. Cancer Inst. 66:1191-1308, 1981.

36. Douglas, J.W.B., and R.E. Waller. Air pollution and respiratory infection in children. Br. J. Prev. Soc. Med. 20:1-8, 1966.

37. Eastcott, D.F. The epidemiology of lung cancer in New Zealand. Lancet 1:37-39, 1956.

38. Ehrlich, R., and M.C. Henry. Chronic toxicity of nitrogen dioxide: I. Effects on resistance to bacterial pneumonia. Arch. Environ. Health 17:860-865, 1968.

39. Eisen, E.A., J.M. Robins, I.A. Greaves, and D.H. Wegman. Selection effects of repeatability criteria applied to lung spirometry. Am. J. Epidemiol. 120:734-742, 1984.

40. Emmerson, B.T. Chronic lead nephropathy. Kidney Int. 4:1-5, 1973.

41. Emmerson, B.T. Chronic lead nephropathy: The diagnostic use of calcium EDTA and the association with gout. Austral. Ann. Med. 12:310-324, 1963.

42. Ferris, B.G. Epidemiology standardization project: II. Recommended respiratory disease questionnaires for use with adults and children in epidemiologic research. Am. Rev. Respir. Dis. 118(Suppl.):7-53, 1978.

43. Ferris, B.G., Jr., F.E. Speizer, J.D. Spengler, D. Dockery, Y.M.M. Bishop, M. Wolfson, and C. Humble. Effects of sulfur oxides and respirable particles on human health: Methodology and demography of populations in study. Am. Rev. Respir. Dis. 120:767-779, 1979.

44. Fletcher, C.M., and R. Peto. The natural history of chronic airflow obstruction. Br. Med. J. 1:1645-1648, 1978.

45. Ford, A.B., and O. Bialik. Air pollution and urban factors in relation to cancer mortality. Arch. Environ. Health 35:350-359, 1980.

46. Gadek, J.E., and R.G. Crystal. α1-Antitrypsin deficiency, pp. 1450-1467. In J.B. Stanbury, J.B. Wyngaarden, D.S. Fredrickson, J.L. Goldstein, and M.S. Brown, Eds. Metabolic Basis of Inherited Disease. New York: McGraw Hill, 1982.

47. Gandevia, B.H. Clinical techniques, pp. 11-33. In H. Weill and M. Turner-Warwick, Eds. Occupational Lung Diseases. New York: Marcel Dekker, Inc., 1981.

48. Gardner, D.E., J.F. Miller, J.W. Illing, and J.M. Kirtz. Increased infectivity with exposure to ozone and sulfuric acid. Toxicol. Lett. 1:59-64, 1977.

49. Gardner, R.M. ATS Statement: Snowbird Workshop on Standardization of Spirometry. Am. Rev. Respir. Dis. 119:831-838, 1979.

50. Gardner, R.M., J.L. Hankinson, and H.W. Glindmeyer, III. Standardization of spirometry with special emphasis in field testing, pp. 61-85. In H. Weill and M. Turner-Warwick, Eds. Occupational Lung Diseases. New York: Marcel Dekker, Inc., 1981.

51. Glindmeyer, H.W., J.E. Diem, R.N. Jones, and H. Weill. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. Am. Rev. Respir. Dis. 125:544-548, 1982.

52. Goetzl, E.J. Asthma: New mediators and old problems. N. Engl. J. Med. 311:252-253, 1984.

53. Golden, J.A., J.A. Nadel, and H.A. Boushey. Bronchial hyperirritability in healthy subjects after exposure to ozone. Am. Rev. Respir. Dis. 118:287-294, 1978.

54. Goldsmith, J.R. The "urban factor" in cancer: Smoking, industrial exposures, and air pollution as possible explanations. J. Environ. Pathol. Toxicol. 3:205-217, 1980.

55. Goldstein, I., and E.M. Dulberg. Air pollution and asthma: Search for a relationship. J. Air Pollut. Control Assoc. 31:370-376, 1981.

56. Goldstein, I.F., and B. Currie. Seasonal patterns of asthma: A clue to etiology. Environ. Res. 33:201-215, 1984.

57. Goyer, R.A., and B. Rhyne. Pathological effects of lead. Int. Rev. Exp. Pathol. 12:1-121, 1973

58. Greenberg, M., D. Barrows, P. Clark, S. Grohs, S. Kaplan, and N. Newton. White female respiratory cancer mortality: A geographical anomaly. Lung 161:235-243, 1983.

59. Greene, S.A., R.K. Wolff, F.F. Hahn, R.F. Henderson, J.L. Mauderly, and D.L. Lundgren. Sulfur dioxide-induced chronic bronchitis in beagle dogs. J. Toxicol. Environ. Health 13:945-958, 1984.

60. Groupe Cooperatif PAARC. Air pollution and chronic or repeated respiratory diseases: II. Results and discussion. Bull. Eur. Physiopathol. Respir. 18:101-116, 1982.

61. Haemisegger, E., A. Jones, B. Steigerwald, and V. Thomson. The Magnitude and Nature of the Air Toxics Problem in the United States. Washington, D.C.: U.S. Environmental Protection Agency, 1984. 100 pp.

62. Haldane, J.B.S. The dissociation of oxyhemoglobin in human blood during partial CO poisoning. Proceedings of the Physiological Society, October 19, 1912. J. Physiol. 45:xxii-xxiv, 1912.

63. Hammond, E.C., I.J. Selikoff, and H. Seidman. Asbestos exposure, cigarette smoking and death rates. Ann. N.Y. Acad. Sci. 330:473-490, 1979.

64. Harlan, W.R., J.R. Landis, R.L. Schmouder, N.G. Goldstein, and L.C. Harlan. Blood lead and blood pressure. J. Am. Med. Assoc. 253:530-534, 1985.

65. Helsing, K.J., G.W. Comstock, F.E. Speizer, B.G. Ferris, M.D. Lebowitz, M.S. Tockman, and B. Burrows. Comparison of three standardized questionnaires on respiratory symptoms. Am. Rev. Respir. Dis. 120:1221-1231, 1979.

66. Henderson, B.E., R.J. Gordon, H. Menck, J. Soohoo, S.P. Martin, and M.C. Pike. Lung cancer and air pollution in southcentral Los Angeles County. Am. J. Epidemiol. 101:477-488, 1975.

67. Higgins, I.T.T. Epidemiologic evidence on the carcinogenic risk of air pollution. INSERM 52:41-52, 1976.

68. Higgins, M. Epidemiology of COPD: State of the art. Chest 85(Suppl.):3S-8S, 1984.

69. Higgins, M.W., J.B. Keller, M. Becker, W. Howatt, J.R. Landis, H. Rotman, J.G. Weg, and I. Higgins. An index of risk for chronic obstructive airways disease. Am. Rev. Respir. Dis. 125:144-151, 1982.

70. Higgins, M.W., J.B. Keller, J.R. Landis, T.H. Beaty, B. Burrows, D. Demets, J.E. Diem, I.T.T. Higgins, E. Lakatos, M.D. Lebowitz, H. Menkes, F.E. Speizer, I.B. Tager, and H. Weill. Risk of chronic obstructive pulmonary disease: Collaborative assessment of the validity of the Tecumseh index of risk. Am. Rev. Respir. Dis. 130:380-385, 1984.

71. Hirayama, T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. Br. Med. J. 282:183-185, 1981.

72. Hogg, J.C., P.T. Macklem, and E.M. Thurlbeck. Site and nature of airway obstruction in chronic obstructive lung disease. N. Engl. J. Med. 278:1355-1360, 1968.

73. Holland, W.W., D.D. Reid, R. Seltser, and R.W. Stone. Respiratory disease in England and the United States: Studies of comparative prevalence. Arch. Environ. Health 10:338-343, 1965.

74. Horvath, S.M., J.A. Gliner, and L.J. Folinsbee. Adaptation to ozone: Duration of effect. Am. Rev. Respir. Dis. 123:496-499, 1981.

75. Hughes, A., C.A. Hughes, and D.T.D. Hughes. Comparison of four spirometers. Thorax 38:228, 1983.

76. Hunt, Jr., W.F., R.B. Faora, and G.M. Duggan. Compilation of Air Toxic and Trace Metal Summary Statistics. Publication No. EPA-450/4-84-015. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1984. 166 pp.

77. Illing, J.W., F.J. Miller, and D.E. Gardner. Decreased resistance to infection in exercised mice exposed to NO_2 and O_3. J. Toxicol. Environ. Health 6:843-851, 1980.

78. Infante, P.F., R.A. Rinsky, J.K. Wagoner, and R.J. Young. Leukemia in benzene workers. Lancet 2:76-78, 1977.

79. International Agency for Research on Cancer. Benzene, pp. 93-148. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs. Vol. 29. Lyons, France: International Agency for Research on Cancer, 1982.

80. Johnson, D.E., J.B. Tillery, and R.J. Prevost. Levels of platinum, palladium, and lead in populations of Southern California. Environ. Health Perspect. 12:27-33, 1975.

81. Johnson, D., and J. Travis. The oxidative inactivation of human α-$_{1}$-proteinase inhibitor. J. Biol. Chem. 254:4022, 1979.

82. Kaliner, M. Hypotheses on the contribution of late-phase allergic responses to the understanding and treatment of allergic diseases. J. Allergy Clin. Immunol. 73:311-315, 1984.

83. Karch, N.J., and M.A. Schneiderman. Explaining the Urban Factor in Lung Mortality. Washington, D.C.: National Resources Defense Council, 1981.

84. Kilburn, K.H., R. Warshaw, and J.C. Thornton. Pulmonary functional impairment and symptoms in women in the Los Angeles Harbor Area. Am. J. Med., 1985. (in press)

85. Knight, L., N.R. Anthonisen, W. Arkinstall, L. Engel, P.T. Macklem, R.R. Martin, L.W. Chakrin, and J.R. Wardell, Jr. The pathophysiology of an animal model for chronic bronchitis. Am. Rev. Respir. Dis. 107:1081-1082, 1973.

86. Knudson, R.J., M.D. Lebowitz, C.J. Holberg, and B. Burrows. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am. Rev. Respir. Dis. 127:725-734, 1983.

87. Kosmider, E., K. Ludyga, A. Misiewice, M. Drozdz, and J. Sagan. Experimentelle und klinische Untersuchungen uber den Einfluss der Stickstoffoxyde auf die Immunität. Int. Arch. Arbeitsmed. 31:9-23, 1973.

88. Kramps, J., C. Franken, and J. Dijkman. ELISA for quantitative measurement of low molecular-weight bronchial protease inhibitor in human sputum. Am. Rev. Respir. Dis. 129:959-963, 1984.

89. Kucich, U., W.R. Abrams, P. Christner, J. Rosenbloom, P. Kimbel, and G. Weinbaum. Molecular weight distribution of elastin peptides in plasmas from human non-smokers, smokers and emphysema patients. Am. Rev. Respir. Dis. 129:307, 1984.

90. Kuhn, C., R.M. Senior, and J.A. Pierce. The pathogenesis of emphysema, pp. 155-198. In H. Witschi and P Nettesheim, Eds. Mechanisms in Respiratory Toxicology. Vol. II. Boca Raton, Fla.: CRC Press, 1982.

91. Kuller, L.H., E.P. Radford, D. Swift, J.A. Perper, and R. Fisher. Carbon monoxide and heart attacks. Arch. Environ. Health 30:477-482, 1975.

92. Landrigan, P.J., S.H. Gehlbach, B.F. Rosenblum, J.M. Shoults, R.M. Candelaria, W.F. Barthel, J.A. Liddle, A.L. Smrek, N.W. Staehling, and J.F. Sanders. Epidemic lead absorption near an ore smelter: The role of particulate lead. N. Engl. J. Med. 292:123-129, 1975.

93. Laskin, S., M. Kuschner, A. Sellakumar, and G.V. Katz. Combined carcinogen-irritant animal inhalation studies, pp. 190-213. In E.F. Aharonson, A. Ben-David, and M.A. Klingberg, Eds. Air Pollution and the Lung. New York: John Wiley and Sons, 1976.

94. Last, J.A., K.M. Reiser, W.S. Tyler, and R.B. Rucker. Long-term consequences of exposure to ozone: I. Lung collagen content. Toxicol. Appl. Pharmacol. 72:111-118, 1984.

95. Laurell, C.B., and S. Eriksson. The electrophoretic α_1-globulin pattern of serum in α_1-antitrypsin deficiency. Scand. J. Clin. Lab. Invest. 15:132, 1963.

96. Lebowitz, M.D., and B. Burrows. Comparison of questionnaires: The BMRC and NHLI respiratory questionnaires and a new self-completion questionnaire. Am. Rev. Respir. Dis. 113:627-635, 1976.

97. Lee, A.M., and J.F. Fraumeni, Jr. Arsenic and respiratory cancer in man: An occupational study. J. Nat. Cancer Inst. 42:1045-1052, 1969.

98. Lindstrom, K. Changes in psychological performances of solvent-poisoned and solvent-exposed workers. Am. J. Ind. Med. 1:69-84, 1980.

99. Linn, W.S., D.A. Fisher, D.A. Medway, U.T. Anzar, D.E. Spier, L.M. Valencia, T.G. Venet, and J.D. Hackney. Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 125:658-663, 1982.

100. Linn, W.S., T.G. Venet, D.A. Shamoo, L.M. Valencia, U.T. Anzar, C.E. Spier, and J.D. Hackney. Respiratory effects of sulfur dioxide in heavily exercising asthmatics: A dose-response study. Am. Rev. Respir. Dis. 127:278-283, 1983.

101. Lioy, P.J., M. Lippmann, and T.A. Vollmuth. Persistence of peak flow decrement in children following ozone exposures exceeding the National Ambient Air Quality Standard. J. Air Pollut. Control Assoc., 1985. (in press)

102. Lippmann, M., P.J. Lioy, G. Liekauf, K.B. Green, D. Baxter, M. Morandi, B. Pasternak, D. Fife, and F.E. Speizer. Effects of ozone on the pulmonary function of children, pp. 423-446. In M.A. Melman, S.D. Lee, and M.G. Mustafa, Eds. Advances in Modern Environmental Toxicology. Vol. V. Princeton, N.J.: Princeton Scientific Publishers, 1983.

103. Lloyd, J.W. Long-term mortality study of steel workers: V. Respiratory cancer in coke plant workers. J. Occup. Med. 13:53-68, 1971.

104. Low, P.M.P., C.K. Luk, M.J. Dulfano, and P. Finch. Ciliary beat frequency of human respiratory tract by different sampling techniques. Am. Rev. Respir. Dis. 130:497-498, 1984.

105. Macklem, P.T., W.M. Thurlbeck, and R.G. Fraser. Chronic obstructive disease of small airways. Ann. Intern. Med. 74:167-177, 1971.

106. Maltoni, C., B. Conti, and G. Cotti. Benzene: A multipotential carcinogen: Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4:589-630, 1983.

107. Maltoni, C., and C. Scarnato. First experimental demonstration of the carcinogenic effects of benzene: Long-term bioassays on Sprague-Dawley rats by oral administration. Med. Lav. 70:352-357, 1979.

108. Matanoski, G.M., E. Landau, J. Tonascia, C. Lazar, E.A. Elliott, W. McEnroe, and K. King. Cancer mortality in an industrial area of Baltimore. Environ. Res. 25:8-28, 1981.

109. Matsuki, J., F. Osaka, H. Kasuga, and M. Sugita. Epidemiological study on the effects of smoking and air pollution using urinary hydroxyproline:creatinine ratio on the healthy schoolchildren and adults. Jap. J. Pub. Health 28:505-515, 1981.

110. McCawley, M., and M. Lippmann. An aerosol disperson test: Comparison of results from smokers and non-smokers, pp. 1007-1010. In B. Liu, D. Pui, and H. Fissan, Eds. Aerosols. New York: Elsevier Science Publishing Co., 1984.

111. McDonnell, W.F., D.H. Horstman, S. Abdul-Salaam, and D.E. House. Reproducibility of individual responses to ozone exposure. Am. Rev. Respir. Dis. 131:36-40, 1985.

112. McDonnell, W.F., D.H. Horstman, M.J. Hazucha, E. Scal, Jr., E.D. Haak, S.A. Salaam, and D.E. House. Pulmonary effects of ozone exposure during exercise: Dose-response characteristics. J. Appl. Physiol. 54:1345-1352, 1983.

113. McGrath, J.J., and C.D. Barnes, Eds. Air Pollution: Physiological Effects. New York: Academic Press, 1982. 353 pp.

114. Mecham, R.P., and G. Lange. Antigenicity of elastin: Characterization of major antigenic determinants on purified insoluble elastin. Biochemistry 21:669-673, 1982.

115. Medical Research Council, Committee on the Aetiology of Chronic Bronchitis. Standardized questionnaires on respiratory symptoms. Br. Med. J. 2:1665, 1960.

116. Melia, R.J.W., C.V. Florey, and S. Chinn. The relation between respiratory illness in primary schoolchildren and the use of gas for cooking: I. Results from a national survey. Int. J. Epidemiol. 8:333-338, 1979.

117. Michaeli, D., and H.H. Fudenberg. Antibodies to collagen in patients with emphysema. Clin. Immunol. Immunopathol. 3:187-192, 1974.

118. Miller, F.J., J.W. Illing, and D.E. Gardner. Effect of urban ozone levels on laboratory-induced respiratory infections. Toxicol. Lett. 2:163-169, 1978.

119. Mittman, C. α1-Antitrypsin deficiency and other genetic factors in lung disease, pp.245-269. In P.T. Macklem and S. Permutt, Eds. The lung in Transition Between Health and Disease. New York: Marcel Dekker Inc., 1979.

120. Morrison, H.I., J. Silins, Y. Mao, M.H. Smith, H. Grant, and D.T. Wigle. Respiratory disease mortality in Canadian mining communities. Chron. Dis. Can. 2:25-29, 1981.

121. Murozomi, M., T.J. Patterson. Chemical concentration of pollutant lead aerosols, terrestial dusts and sea salts in Greenland and Antarctic snow strata. Geochim. Cosmochim. Acta 33:1247-1294, 1969.

122. National Research Council, Committee on Biologic Effects of Atmospheric Pollutants. Lead: Airborne Lead in Perspective. Washington, D.C.: National Academy of Sciences, 1972. 330 pp.

123. Needleman, H.L., C. Gunnoe, A. Leviton, R. Reed, H. Peresie, C. Maher, and P. Barrett. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300:689-695, 1979.

124. Needleman, H.L., A. Leviton, and D. Bellinger. Lead-associated intellectual deficit. N. Engl. J. Med. 306:367, 1982.

125. Niejadlik, D.C. Sputum, pp. 523-536. In J.B. Henry, Ed. Clinical Diagnosis and Management by Laboratory Methods. Philadelphia: W.B. Saunders, Co., 1984.

126. Niewoehner, D.E., J. Kleinerman, and D.B. Rice. Pathologic changes in the peripheral airways of young cigarette smokers. N. Engl. J. Med. 291:755-758, 1974.

127. Nilsen, A.M., and S Engen. Statistical derivation of a standardized procedure for counting expectorated alveolar macrophages as indicators of occupational air pollution. Br. J. Ind. Med. 42:205-208, 1985.

128. Nisbet, I.C.T., M.A. Schneiderman, N.S. Karch, and D.M. Siegel. Review and Evaluation of the Evidence for Cancer Associated with Air Pollution. Publication No. EPA-450/5-83-006. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1983. 295 pp.

129. Nobutomo, K. Air pollution and cytological changes in sputum. Lancet 1:523-526, 1978.

130. Ott, G. M., J.C. Townsend, W.A. Fishbeck, and R.A. Langner. Mortality among individuals occupationally exposed to benzene. Arch. Environ. Health 33:3-10, 1978.

131. Patterson, R., and R.A. Goldstein, Eds. Symposium Proceedings on Occupational Immunological Lung Disease, February 25, 1982. J. Allergy Clin. Immunol. 70:1-72, 1982.

132. Pelham, F., M. Wewers, and R. Crystal, and A. Janoff. Urinary desmosine excretion in normal patients with homozygous alpha 1-antitrypsin deficiency. Am. Rev. Respir. Dis. 129:307, 1984.

133. Percy, C., E. Stanek, III, and L. Gloeckler. Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am. J. Public Health 71:242-250, 1981.

134. Perera, F.P., and I.B. Weinstein. Molecular epidemiology and carcinogen-DNA adduct detection: New approaches to studies of human cancer causation. J. Chron. Dis. 35:581-600, 1982.

135. Pershagen, G., C.G. Elinder, and A.M. Bolander. Mortality in a region surrounding an arsenic emitting plant. Environ. Health Perspect. 19:133-137, 1977.

136. Pham, Q.T., A.M. Bess, J.M. Mur, P. Sadoul, and J. Haluskza. Follow-up study of construction workers with obstructive lung disease. Scand. J. Respir. Dis. 58:215-226, 1977.

137. Picciano, D. Cytogenetic study of workers exposed to benzene. Environ. Res. 19:33-38, 1979.

138. Pirkle, J.L., J. Schwartz, J.R. Landis, and W.R. Harlan. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121:246-258, 1985.

139. Port, C.D., K.V. Ketels, D.L. Coffin, and P. Kane. A comparative study of experimental and spontaneous emphysema. J. Toxicol. Environ. Health 2:589-604, 1977.

140. Quanjer, Ph.H., Ed. Lung Function Testing. Bull. Europ. Physiopathol. Respir. 19(Suppl.5):1-96, 1983.

141. Radford, E.P., and T.A. Drizd. Blood carbon monoxide levels in persons 3-74 years of age: United States 1976-80. National Center for Health Statistics Advance Data Report No. 76. DHHS Publication No. (PHS) 82-1250. Washington, D.C.: U.S. Department of Health and Human Services, 1982.

142. Reid, D.D., J. Cornfield, R. Markush, D. Siegel, E. Pedersen, and W. Haenszel. Studies of disease among emigrants and native populations in Great Britain, Norway and the United States: III. Prevalence of cardiorespiratory symptoms among migrants and native-born in the United States, pp. 321-346. NCI Monograph No. 19. Bethesda, Md.: U.S. Department of Health, Education, and Welfare, National Cancer Institute, 1966.

143. Rinsky, R.A., R.J. Young, and A.B. Smith. Leukemia in benzene workers. Am. J. Ind. Med. 2:217-245, 1981.

144. Samet, J.M., I.B. Tager, and F.E. Speizer. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am. Rev. Respir. Dis. 127:508-523, 1983.

145. Schachter, E.N., T.J. Witek, G.J. Beck, H.R. Hosein, C. Colice, B.P. Leaderer, and W.S. Cain. Airway effects of low concentrations of sulfur dioxide. Arch. Environ. Health 39:34-42, 1984.

146. Seppalainen, A.M., K. Husman, and C. Martenson. Neurophysiologic effects of long-term exposure to a mixture of organic solvents. Scand. J. Work Environ. Health 4:304-314, 1978.

147. Shear, C.L., D.B. Seale, and M.S. Gottleib. Evidence of space-time clustering of lung cancer deaths. Arch. Environ. Health 35:335-343, 1980.

148. Silverberg, E. Cancer Statistics, 1985. CA 35:19-35, 1985.

149. Smith, M., T. Delves, R. Lansdown, B. Clayton, and P. Graham. The Effects of Lead Exposure on Urban Children: The Institute of Child Health/ Southampton Study. Dev. Med. Child Neurol. Supplement No. 47, 1983. 54 pp.

150. Snyder, C.A., B.D. Goldstein, A.R. Sellakumar, I. Bromberg, S. Laskin, and R.E. Albert. The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57BL/6J mice. Toxicol. Appl. Pharmacol. 54:323-331, 1980.

151. Solic, J.J., M.J. Hazucha, and P.A. Bromberg. The acute effects of 0.2 ppm ozone in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 125:664-669, 1982.

152. Soskolne, C.L., E.A. Zeighami, N.M. Hanis, L.L. Kupper, N. Herrmann, J. Amsel, J.S. Mausner, and J.M. Stellman. Laryngeal cancer and occupational exposure to sulfuric acid. Am. J. Epidemiol. 120:358-369, 1984.

153. Speizer, F.E. Assessment of the epidemiological data relating lung cancer to air pollution. Environ. Health Perspect. 47:33-42, 1983.

154. Tager, I.B., S.T. Weiss, A. Munoz, B. Rosner, and F.E. Speizer. Longitudinal study of maternal smoking and pulmonary function in children. N. Engl. J. Med. 309:699-703, 1983.

155. Taylor, J.C., and L. Oey. Ceruplasmin: Plasma inhibitor of the oxidative inactivation of alpha$_1$-protease inhibitor. Am. Rev. Respir. Dis. 126:476-482, 1982.

156. Thurlbeck, W.M. Chronic Airflow Obstruction in Lung Disease. Philadelphia, Pa.: W.B. Saunders Company, 1976. 456 pp.

157. Thurlbeck, W.M. The pathobiology and epidemiology of human emphysema, pp. 143-164. In F.J. Miller and D. B. Menzel, Eds. Fundamentals of Extrapolation Modeling of Inhaled Toxicants. Washington, D.C.: Hemisphere Publications Corp., 1984.

158. Travis, J., and G.S. Salvesen. Human plasma proteinase inhibitors. Ann. Rev. Biochem. 52:655-709, 1983.

159. Turino, G.M. Effects of carbon monoxide on the cardiorespiratory system. Carbon monoxide toxicity: Physiology and biochemistry. Circulation 63:253A-259A, 1981.

160. U.S. Centers for Disease Control. Preventing Lead Poisoning in Young Children. Atlanta, Ga.: U.S. Department of Health and Human Services, Centers for Disease Control, 1985. 35 pp.

161. U.S. Department of Health and Human Services. The Health Consequences of Smoking: Chronic Obstructive Lung Disease, p. 83. A Report of the Surgeon General. Rockville, Md.: U.S. Department of Health and Human Services, Office on Smoking and Health, 1984.

162. U.S. Environmental Protection Agency. Air Quality Criteria for Lead. Publication No. EPA-600/8-77-017. Washington, D.C.: U.S. Environmental Protection Agency, 1977. 299 pp.

163. U.S. National Cancer Institute. SEER Program: Cancer Incidence and Mortality in the United States, 1973-1981. NIH Publication No. 85-1837. Bethesda, Md.: U.S. Department of Health and Human Services, National Cancer Institute, 1984. 330 pp.

164. U.S. National Center for Health Statistics. Advance Report of Final Mortality Statistics, 1982. Monthly Vital Statistics Report. Vol. 33, No. 9 (Supplement). Publ. No. (PHS)85-1120. Hyattsville, Md.: U.S. Deparment of Health and Human Services, National Center for Health Statistics, 1984. 43 pp.

165. U.S. National Center for Health Statistics. Monthly Vital Statistics Report, p. 19. Vol. 32, No. 13. DHHS Publ. No. (PHS) 84-1120. Hyattsville, Md.: U.S. Department of Health and Human Services, National Center for Health Statistics, 1984.

166. U.S. National Center for Health Statistics. National Death Index: User's Manual. DHHS Publication No. (PHS)81-1148. Hyattsville, Md.: U.S. Department of Health and Human Services, National Center for Health Statistics, 1981. 42 pp.

167. U.S. National Institute of Environmental Health Sciences. Biochemical and cellular markers of chemical exposure and preclinical indicators of disease. In Human Health and the Environment: Some Research Needs. Research Triangle Park, N.C.: U.S. National Institute of Environmental Health Sciences, 1985. (in press)

168. Van der Lende, R., T.J. Kok, R.P. Reig, Ph.H. Quanjer, J.P. Schouten, and N.G.M. Drie. Decreases in VC and FEV_1 with time: Indicators for effects of smoking and air pollution. Bull. Eur. Physio-pathol. Respir. 17:775-792, 1981.

169. Vogel, J.A., and M.A. Gleser. Effects of carbon monoxide on oxygen transport during exercise. J. Appl. Physiol. 32:234-239, 1972.

170. Wagoner, J.K., R.W. Miller, F.E. Lundin, Jr., J.F. Fraumeni, Jr., and M.E. Haij. Unusual cancer mortality among a group of underground metal miners. N. Engl. J. Med. 269:284-289, 1963.

171. Walker, R.D., T.H. Connor, E.J. MacDonald, N.M. Treiff, M.S. Legator, K.W. MacKenzie, and J.G. Dobbins. Correlation of mutagenic assessment of Houston air particulate extracts in relation to lung cancer mortality rates. Environ. Res. 28:303-312, 1982.

172. Ware, J.H., D.W. Dockery, A. Spiro, III, F.E. Speizer, and B.G. Ferris, Jr. Passive smoking, gas cooking, and respiratory health of children living in six cities. Am. Rev. Respir. Dis. 129:366-374, 1984.

173. Whittemore, A.S., and E.L. Korn. Asthma and air pollution in the Los Angeles Area. Am. J. Pub. Health 70:687-696, 1980.

174. Yan, K., C. Salome, and A.J. Woolcock. Rapid method for measurement of bronchial responsiveness. Thorax 38:760-765, 1983.

175. Yanagisawa, Y., H. Matsuki, and H. Kasuga. Personal exposure and health effect relation for NO_2 with urinary hydroxyproline to creatinine ratio as indicator. Arch. Environ. Health, 1985. (in press)

176. Yule, M., and M. Rutter. Effects of lead on children's behavior and cognitive performance: A critical review. In K.R. Mahaffey, Ed. Dietary and Environmental Lead: Human Health Effects. Amsterdam: Elsevier Science Publishing Co., 1985. (in press)

177. Zamel, N., M.D. Altose, and W. Speir, Jr. Statement on spirometry: American College of Chest Physicians scientific section recommendations. Chest 83:547-550, 1983.

Chapter 3

Exposure Assessment

3

EXPOSURE ASSESSMENT

INTRODUCTION

This chapter discusses the relationship of exposure assessment to the design and conduct of epidemiologic studies of air pollution. After presenting a working definition of exposure assessment, it discusses the pertinent history of air pollution monitoring and a framework for contemporary exposure assessment. The chapter then identifies the types of pollutants that the Committee feels require attention, indicating some physical, chemical, and spatiotemporal properties that are relevant to exposure assessment. Sections on special approaches to indoor pollutants and monitoring considerations follow, including opportunities for providing optimal exposure data in future epidemiologic studies. Finally, several important characterization studies are reviewed.

Exposure assessment refers to a set of multidisciplinary activities that describe who is exposed to how much of what substances, for how long, and under what conditions.[14] Exposure assessment, whether based on direct measurement or modeling, is a vital part of all environmental epidemiology. Exposure assessment of air pollutants is particularly complex, because pollutants do not occur independently, but as mixes of natural, industrial, transportation, and residential emissions. The focus of interest in this chapter is human exposure. Hazards to the environment, such as from acid deposition, are important, but are not the subject of this report.

In an epidemiologic study, exposure assessment can be addressed before, during, and after the collection of health effects data. Conducted beforehand, it can lead to improvement in study design by treating the issues of subject selection, sample size, scale and frequency of monitoring, and usefulness of such tools as fixed-site monitors and descriptive questionnaires. Exposures can then be remeasured, in conjunction with health effects measurement, to provide a basis for a quantitative estimate of the association between exposure and effect.

Exposure assessment has many purposes in air pollution research aside from providing exposure variable measurements for epidemiologic studies. Independent and parallel efforts to describe exposure may aim, for example, to determine the effectiveness of efforts to lower exposures, compare possible risks between various populations with different exposure conditions, develop siting and timing strategies for routine ambient air monitoring, and weigh the importance of various components of multisource and multimedium exposures. Obviously, some of these functions require assumptions about quantitative risk relationships based on previous health effects studies. Also, rather than incorporate new exposure assessment and costs into each epidemiologic study, we can often rely on information and assumptions derived from well-designed, independently conducted exposure assessment research.

The central theme of this chapter is that the integration of exposure assessment into an epidemiologic study and the decisions as to which aspects of exposure assessment to emphasize will depend on the nature of the specific research question. To be effective under current conditions, exposure assessment in air pollution epidemiology must be flexibly based on reasonable biologic modeling of exposure and effect and must comprise the degree of detail required by the research question. Thus, environmental monitoring should not be restricted arbitrarily from the outset to indoor or outdoor sources or to fixed or personal monitors.

The advance in measurement technology increases the variety of potential epidemiologic studies, but does not in itself provide a valid rationale for a given study. The mere ability to measure exposure to a pollutant precisely is not a sufficient reason to launch a study; indeed, many studies that are possible might be unimportant or of unlikely productivity.

The ultimate goal of exposure assessment in epidemiologic studies of air pollution is to minimize the misclassification of study subjects by exposure magnitude or type. Common variations in outdoor and indoor concentrations and the proportions of time people spend in different locations can yield substantial overlap in the true total exposure between subjects assigned to high- and low-exposure groups. This applies whether exposure magnitude is assigned on the basis of categorical descriptor variables or ambient monitoring from central stations. Misclassification is a major reason for loss of sensitivity in such studies; it increases the likelihood that a study will fail to detect a real association between an air pollution exposure and a health effect. The problem of exposure misclassification is described in more detail in Appendix C and several recent papers.[6,10,18]

EXPOSURE, DOSE, AND BIOLOGIC MARKERS

Most epidemiologic studies of air pollution have assumed that exposure, however measured, constitutes an adequate surrogate of the dose of a given pollutant. Recent advances in toxicology and molecular epidemiology have clarified the meaning of these terms and emphasized some important distinctions.[56] "Exposure" (see Figure 1) commonly refers to concentrations of pollutants measured in the environment. As to dose itself, two distinctions can be made: "internal dose" is the amount of a substance or its metabolites in body tissues, and "biologically effective dose" is the amount that interacts with a particular target tissue or its surrogate.[14] In this report, however, "exposure," unless otherwise specified, refers to all kinds of exposure, from ambient air to critical target organ. Research is required to relate a specific ambient exposure to the dose received by a given target tissue in the respiratory tract and to relate that dose, in turn, to a specific health effect. This research will ultimately benefit future epidemiologic studies of air pollution.

One of the major constraints in determining the relationship between exposure to air pollutants and the development of nonneoplastic diseases of the respiratory tract is the lack of biologic markers of exposure. Biologic markers that would indicate the cumulative dose of specific pollutants or types of pollutants to the

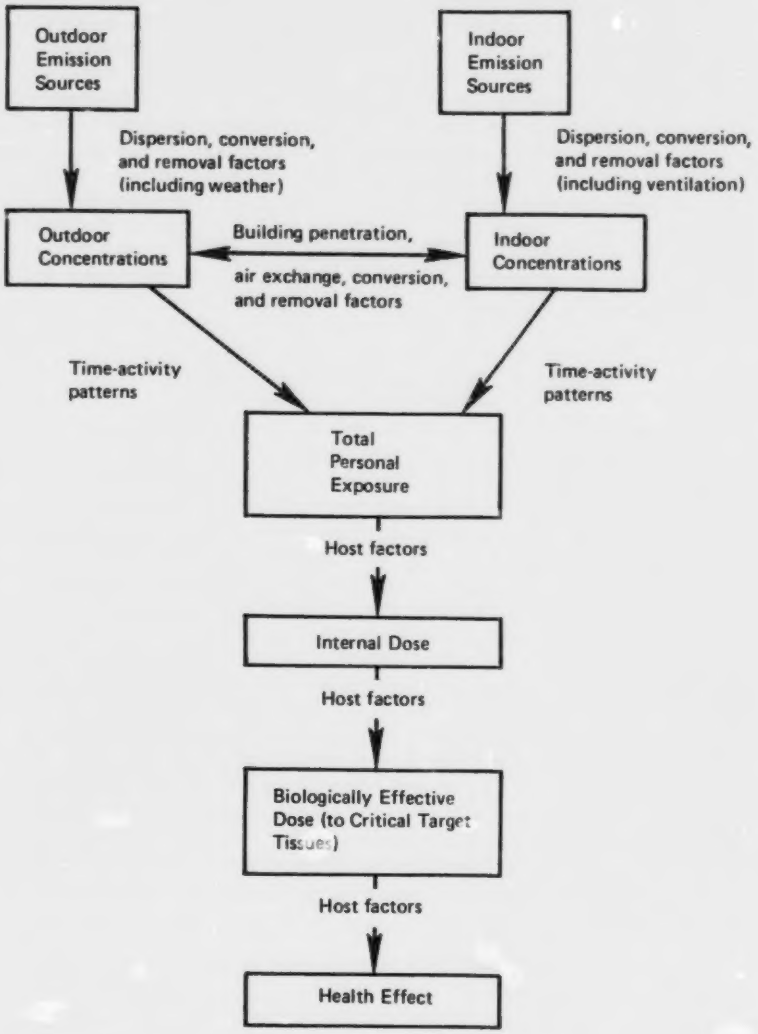

Outdoor Emission Sources
Indoor Emission Sources
Dispersion, conversion, and removal factors (including weather)
Dispersion, conversion, and removal factors (including ventilation)
Outdoor Concentrations
Building penetration,
air exchange, conversion, and removal factors
Indoor Concentrations
Time-activity patterns
Time-activity patterns
Total Personal Exposure
Host factors
Internal Dose
Host factors
Biologically Effective Dose (to Critical Target Tissues)
Host factors
Health Effect

FIGURE 1 Framework for exposure assessment.

respiratory tract would be invaluable in determining precise relationships between exposures and disease.

HISTORICAL BACKGROUND

As analytic techniques became available around the turn of the century, air pollution investigations moved beyond crude and subjective forms of exposure assessment (e.g., number of foggy days, amount of coal use, or distance from emission sources) to measurement of pollution surrogates, such as dust fall or total acidity. Air monitoring in major European cities for sulfur dioxide, SO_2, and smoke began in the 1930s. In the United States, federally sponsored surveys of urban air pollution began in the middle 1950s, and routine monitoring was common by the late 1960s. Today, air pollution monitoring is a highly developed field of applied science. Sophisticated analytic devices are available for measuring many contaminant gases continuously; and particles can be separated by size and analyzed for chemical composition (see box on instrumentation).

However, many of the established air pollution monitoring networks were not designed to test explicit biologic models of the health effects of air pollution. Pollutant monitoring typically provided averaged concentration data, usually over 24 hours or a full year, except for hourly data on ozone, O_3, and carbon monoxide, CO. Cumulative exposure, frequency of concentration peaks, lag effects, and combined pollutant exposure indexes could not be explored in the air pollution epidemiology of the 1940s, 1950s, and 1960s. Current standards for SO_2 and total suspended particles (TSP), based on past data, can thus be surrogates for other exposure times or pollutant species that are really responsible for the effects of concern. Likely candidates include size-fractionated particles and acid aerosols and gases.

Until very recently, most air pollution epidemiology investigated relationships between adverse health outcomes in a population and average ambient air pollution concentrations. Most often, data from relatively few central outdoor monitoring stations were used to represent the exposure of all subjects in an entire residential community. Indoor sources that could contribute to total personal exposures to many of the

A NOTE ON AVAILABLE INSTRUMENTATION

Since the early 1970s, instruments and techniques for monitoring exposure to air pollutants have grown substantially in sophistication. Many types of continuous and integrating (discrete period) samplers have been developed for use in a variety of situations, both indoors and outdoors, and they are easily adaptable for providing data on cumulative exposure, time-lagged responses, and frequency of periodic exposure peaks. Quantitative chemical analysis now offers precision and sensitivity far greater than those required for most epidemiologic studies.

Personal monitors are available in two basic types: active monitors, which use a pump to draw a measured volume of air into a collecting medium; and passive monitors, which are small lightweight badges that sample by passive diffusion of chemicals. The recent rapid development of diffusion badges is particularly notable, because they have become inexpensive and inconspicuous enough to be used for large populations. However, personal monitors are still all of the integrating type; the choices of sampling and averaging times are limited by available instrumentation. Detailed information on specific equipment can be found elsewhere.[15] [31]

pollutants encountered outdoors were rarely considered. Studies implicitly assumed that the differences in outdoor concentrations of some pollutants between cities or between regions within a community were more important determinants of individual or population exposures than housing or other personal factors. In past decades, when outdoor concentrations in many urban areas were higher than today, they might in fact have been the most important determinants of population exposure to SO_2, TSP, benzo[a]pyrene (BaP), and other major industrial and utility-derived pollutants. If differences in exposure within groups are small, compared with differences between groups, the use of fixed monitors at representative sites in the community might suffice. But pollutants with important indoor sources or sharp variations in outdoor concentrations from place to place within people's daily mobility range could yield large differences in exposures within groups and require some incorporation of personal measuring techniques. Therefore, although outdoor ambient measurements might still be appropriate for some current questions in air pollution epidemiology, future studies will have to look at exposure in a more sophisticated context.

FRAMEWORK FOR EXPOSURE ASSESSMENT

In the last decade, recognition of the complexity of the determinants of individual exposure to air pollutants and the impact of misclassification has led to the need for a new conceptual framework for exposure assessment. Figure 1 depicts the relationship of indoor and outdoor pollutant sources and concentrations to each other and to total personal exposure. "Total personal exposure" refers here not only to the total, time-integrated cumulative exposure, but to the number and character of significant peak exposures, because in air pollution studies exposure assessment can develop from a biologic model of the exposure-effect relationship that involves cumulative exposures, peak exposures, or both. We are beginning to understand the interaction of key factors in determining total exposure to some pollutants. Outdoor emission sources contribute to outdoor concentrations, which in turn penetrate to a degree into indoor environments; and indoor sources also contribute to indoor concentrations. The relative importance of indoor and outdoor concentrations in determining personal exposure (average or peak) to a given pollutant depends on several factors, including the location of the predominant source of the pollutant, the daily time-activity patterns of exposed people, other host factors, and the pollutant's entry into, mixing in, and removal from a structure. More detail on the impact of indoor pollutants on air pollution epidemiology will be provided in a later section.

With our present knowledge, we can divide air pollutants into three categories by source:

- Outdoor, e.g., SO_2, sulfates, O_3, and lead.

- Outdoor and indoor, e.g., fine particles, nitrogen dioxide, and CO.

- Indoor, e.g., volatile organic chemicals, formaldehyde, woodsmoke, and radon.

Of course, these categories might not apply in exceptional situations, such as in communities near industrial point sources.

Total personal exposure to an air pollutant is a conceptually important measure for epidemiology. Among the exposure measures that are practically attainable, total personal exposure is the most valid predictor of the risk of any air-pollution-related health effect in a given person. Ideally, perfect individual exposure data (with no misclassification) could come only from measurement of biologically effective personal dose (see Figure 1). All methods of measuring individual exposure are essentially surrogates and can be ranked according to their crudeness or likelihood of misclassification error:

- Total personal exposure: direct personal monitoring in breathing zone.
- Total personal exposure: indirect area monitoring.
- Predictive models using questionnaire and other data.
- Questionnaire data (categorical descriptors) without modeling.

To assess total personal exposure to air pollutants, one can sample near the breathing zone of the subject with portable instruments or one can find the time-weighted sum of concentrations measured in a series of locations in which the subject spends the day. The latter, indirect approach requires time-activity logs and portable area monitors (rather than smaller monitors that are worn) for measuring microenvironmental concentrations.

It is important to distinguish between direct measurement and indirect estimations of total personal exposure. Indirect estimations necessarily assume that contaminant concentrations within the microenvironment are uniform--for example, that within an office or a particular room in a home the concentration measured at one point accurately represents the entire small area. However, multiple measurements often reveal widely varied concentrations within a microenvironment. The design of a monitoring program can mitigate this oversimplication to some extent.

Research is also underway to improve the statistical handling of data from indirect personal exposure assessment and to resolve unexplained discrepancies with direct measurements. It might ultimately be more practical and cost-effective to pursue the indirect estimation approach for some epidemiologic studies, inasmuch as accurate, inconspicuous, and affordable personal monitors are not available for all pollutants and quality control of personal monitoring is more difficult than that of area monitoring. Furthermore, on the basis of the pollutants involved, a substantial fraction of the variance in human exposures might be explained by monitoring in relatively few locations.

As the complex interaction of the variables becomes clarified in exposure assessment research, accurate predictive models for estimating average or peak exposures can be developed for some types of pollutants.[28] These models, which can use various kinds of data to minimize the need for actual measurements, are potentially applicable to epidemiologic studies. Future studies might use combinations of measurement and modeling approaches.

Several factors can modify personal exposure or dose and should be addressed in planning exposure assessment for epidemiologic studies:

- Activity: The amount of an air pollutant inhaled depends in part on ventilatory rate. Exercise or manual work can influence total dose.

- Respiratory tract anatomy and physiology: The relationships among lung volume, ventilatory rate, and body size vary with age and race. Infants have a high ratio of ventilation to body size and can therefore have greater pollutant dose per unit of tissue than older people. The accessibility of various sensitive regions of the lung to pollutants also varies between persons. A smoker with a damaged mucociliary mechanism might receive a greater dose from a given ambient exposure than a nonsmoker.

- Weather: Meteorologic conditions can affect the concentrations of pollutants, including those formed after emission of precursors. Weather also can produce some respiratory changes that are similar to those produced by pollutants. Climate has obvious effects on activity patterns and on housing characteristics that influence air exchange.

Not all epidemiologic studies on air pollution require measurement of total personal exposure. Personal monitoring itself is an option, rather than a prerequisite, for good exposure assessment. Chapter 4 discusses the actual role of personal monitoring in epidemiologic studies on air pollution. Here it need be stated only that the current framework for viewing total exposure offers more precision and improved flexibility in choosing where to measure air pollution and therefore demands more careful planning.

SOME POLLUTANTS OF CONCERN

PHYSICAL, CHEMICAL, AND BIOLOGIC CHARACTERIZATION

Planning of epidemiologic studies requires information on the composition of ambient air in the communities of interest and its variation over space and time. Prior assessment of ambient concentrations can help to define the populations potentially exposed to the contaminants of interest; in some instances, potentially confounding pollutant patterns or other variables can be identified. The degree of prior assessment varies widely, but sometimes it involves obtaining detailed information about the chemical, physical, or even biologic nature of the air in a community.

Some emission is "fresh" from local sources; some is "aged" from distant sources. Reactive and unreactive compounds undergo changes in the atmosphere after emission. Most notable is the photochemical transformation of nitrogen oxides and hydrocarbons to O_3 and other photochemical oxidants. Some gases are oxidized to aerosol species, such as SO_2 to aerosol sulfate, SO_4^{-2} and nitrogen dioxide, NO_2, to aerosol nitrate, NO_3^{-2}. Wet and dry deposition processes alter the concentration and composition of ambient pollutants. Because emission patterns and the meteorology of transport, transformation, and dispersion vary temporally, as well as spatially, most epidemiologic studies must carefully characterize several pollution-related variables in addition to the contaminant of interest. Prior assessment of this nature can help to reduce the scope of effort required in a study. A review of several characterization studies appears at the end of this chapter.

The mix of pollutants in the environment includes some "older" regulated pollutants that still present stubborn problems and other, newly emerging or previously ignored pollutants that require attention. The pollutants vary in several critical ways: from primary emission to secondary product, from outdoor source to indoor source or both, from presenting a direct health threat to indicating other pollutants, and from spreading over vast areas to accumulating in specific microenvironments.

Pollutants known to be sufficiently widespread or present in sufficiently high concentrations to warrant study in future epidemiologic investigations include:

- Acid aerosols, acid gases, and O_3.
- NO_2.
- CO.
- Lead.
- Radon and its progeny.

Emerging classes of pollutants that might require epidemiologic and exposure studies include:

- Volatile organic chemicals (VOCs) and products of incomplete combustion (PICs) from new or reintroduced sources.

Some aspects of these six classes that are relevant for planning of future studies are discussed below.

ACID AEROSOLS, ACID GASES, AND OZONE

For the secondary pollutants O_3 and acid aerosol (for example, sulfuric acid, H_2SO_4, and ammonium bisulfate, NH_4HSO_4), the primary source of human exposure is the outdoor environment. Acid aerosol particles constitute a highly variable fraction of a regulated pollutant--particulate matter. Almost all acid aerosol is included in the fine particle (FP) and particulate matter 10 (PM_{10}) fractions, although FP and PM_{10} measurements alone do not differentiate among the inorganic and organic compounds that make up particulate mass.* Recent data, from both laboratory and epidemiologic studies, have suggested that SO_4^{-2} in ambient air can be a particular cause for concern.[16, 58]

Ambient concentrations of O_3 and SO_4^{-2} can be highly correlated and relatively uniform over very large geographic areas in the summer and have the potential for affecting large segments of the population downwind of areas of precursor emission, particularly during major regional photochemical smog episodes.[9, 23, 35, 45, 63] However, during such episodes, the distribution and speciation of H_2SO_4, NH_4HSO_4, and the fully neutralized ammonium sulfate, $(NH_4)_2SO_4$ (in decreasing order of presumed toxicity), have not been examined in a systematic fashion. Therefore, examination of the areas where SO_4^{-2} makes up a substantial portion of FP and PM_{10} and where widespread exposure to H_2SO_4 can occur should define the best opportunities for epidemiologic investigations.

Mapping of changes in ozone concentrations in the Northeast over a single day has indicated (see Figure 2) that nonurban areas downwind of New York City receive the highest episodic ozone exposures and that locations farthest from this source of precursor emission reach their peak ozone concentrations latest in the day.[8] Movement of photochemical plumes is determined in part by meteorologic conditions, such as prevailing windspeed and wind direction. These and other observations concerning the spatiotemporal characteristics of O_3 transport should be considered in determining the selection of populations and the timing of health effects measurements in epidemiologic studies.

---

*The FP fraction consists of particles less than 2.5 μm in aerodynamic diameter, and the PM_{10} fraction, particles of 10 μm or less in aerodynamic diameter. Both PM_{10} and FP can be easily inspired deep into the lung.

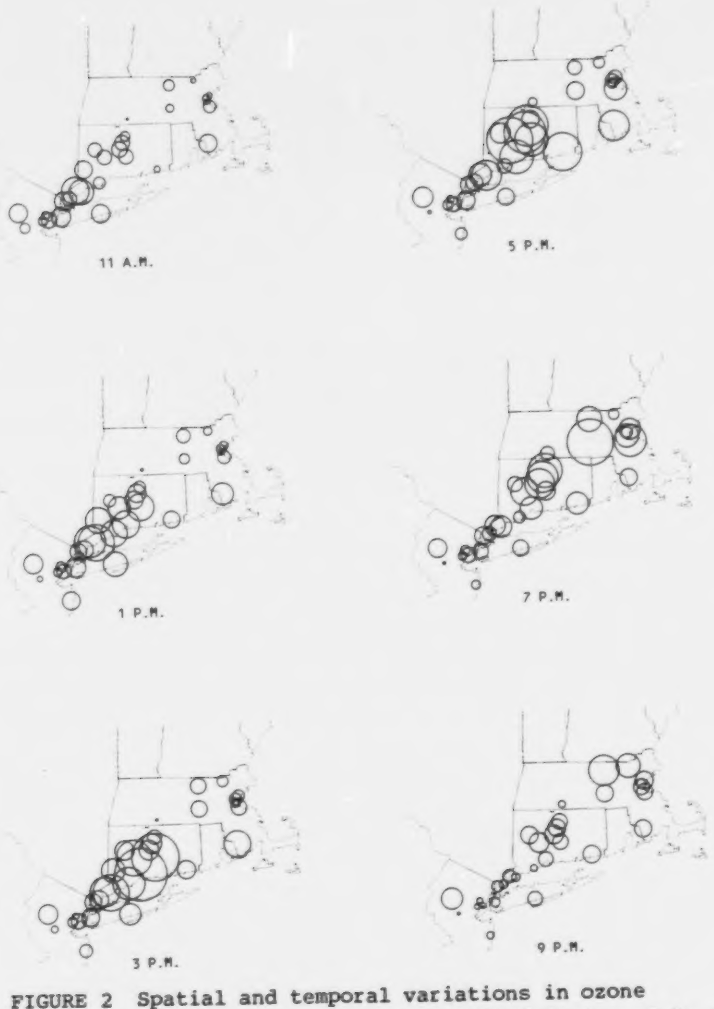


FIGURE 2 Spatial and temporal variations in ozone concentrations in the northeastern United States, July 2, 1974. During summer, when winds from the Southwest commonly prevail, daily movement of photochemical activity is from the New York City region into southern New England. Ozone concentrations are proportional to circle diameters. Reprinted with permission from Cleveland et al.[8]

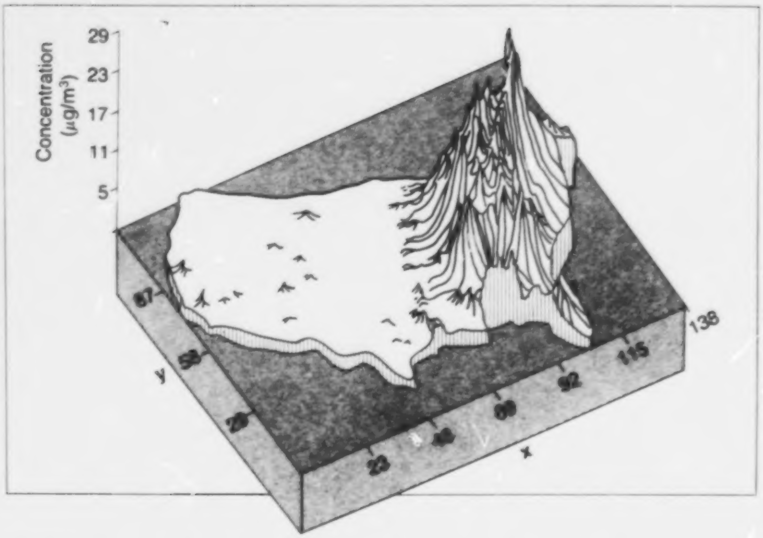


FIGURE 3 Predicted annual sulfate concentrations in 1990 from the Brookhaven long-distance transport model. Emissions are from major coal-burning facilities and include area sources. Sulfate concentrations are proportional to altitude and spatially averaged over 32 x 32-km grids (x,y). Reprinted with permission from Wilson *et al.*[62]

Predicted annual concentration patterns of SO_4^{-2} (Figure 3) indicate that the eastern third of the coterminous United States will be substantially exposed and that the exposure will contrast sharply with that in other parts of the country. In winter and in the presence of specific meteorologic conditions, such as plume fumigation (downward diffusion of stack emission) and fog, primary acidic particulate sulfate can exist independently of O_3. However, in such circumstances, the areas selected for study would probably be much smaller than those selected in summer smog episodes and include urban centers or areas downwind of power plants.

Exposures to acid aerosols and O_3 are modified in accord with the ability of each pollutant to penetrate indoors (e.g., air-conditioned versus non-air-conditioned environments during the summer) and to react with surfaces and with other indoor air contaminants. O_3 in particular is rapidly dissipated after contact with textured indoor surfaces, such as rugs, curtains, books, and furniture.[39] The accumulation of O_3 outdoors usually results from a complex series of photochemical reactions that produces other irritant species (aldehydes, peroxyacetylnitrate, etc.). The Environmental Protection Agency has established continuous monitoring networks to determine compliance and detect the presence of O_3 in nonurban and urban areas throughout the country. However, concern over potential health effects in groups spending large portions of the summer day outdoors during periods of maximal O_3 and SO_4^{-2} exposure will require adjustments in monitor locations for epidemiologic purposes.

NITROGEN DIOXIDE

NO_2 exposure poses different problems for epidemiologic research. Personal exposure to NO_2 can have both indoor and outdoor components, with the highest exposures occurring indoors in the presence of unvented combustion sources (e.g., gas stoves).[41] A systematic investigation of the health effects of short-term and chronic exposures to NO_2 in summer and winter is required. The study designs must include examination of a variety of microenvironments that have and do not have indoor sources of NO_2.

CARBON MONOXIDE

The measurement of CO exposure presents design questions similar to those presented by NO_2 measurement, in that both outdoor and indoor sources typically are present. Recent studies of total exposure to CO in Boston, Denver, and Washington, D.C., have indicated a lack of association between outdoor CO concentration and personal-monitor measurements based on diffusion badges.[24, 65] Personal monitors for CO are reliable, but broader studies of exposure are needed to define populations at risk. Typical and extreme case studies of temporal and spatial variations are required for examination of short-term effects and accumulated burdens and for relation of these exposures to changes in carboxyhemoglobin, a well-validated biologic marker of exposure.

LEAD

The study of lead as a pollutant of epidemiologic concern requires careful consideration of both indoor and outdoor environments. The populations for study could be large, because of the continued presence of lead in gasoline. Inasmuch as average blood lead concentrations have decreased from 1976 through 1980 with the national decrease in lead in gasoline, it will be important to study whether additional declines are associated with the phased-in reduction of lead in gasoline. Future air pollution studies on lead in the United States must also focus on individual point sources, such as smelters.[3] Outdoor measurements could well be needed at sites other than a centralized monitoring station; for instance, recent data suggest that people can be substantially exposed to airborne lead in motor vehicles.[54] Future studies of environmental lead exposure should differentiate the relative contributions of water, food, workplace, and other sources to total lead exposure, as reflected by such measures as blood or dentin lead.

RADON AND ITS PROGENY

Radon and its decay products are of much concern, because radon is a primary indoor air pollutant and has common natural environmental sources, such as the earth surrounding residences, building materials used to construct homes, and water that enters homes.[36] [37] The problem has grown since the 1970s, as homeowners have sealed residential structures to reduce energy consumption. Some investigations of radon exposure will require study sites with maximal potential for exposure (i.e., homes in potential radon hot spots in the earth's crust), and others should be based on representative cross sections of the housing stock in the United States. Estimates of exposures of select populations with high exposures are available, but estimates that are more representative of the general population are needed. Studies of radon exposure should include samples integrated over the course of an entire year.

VOLATILE ORGANIC CHEMICALS AND PRODUCTS OF INCOMPLETE COMBUSTION

VOCs and PICs--large groups of materials that can be toxic, carcinogenic, or both--are associated with small and increasingly numerous sources. An estimated 11 million American homes are now heated at least partially by wood fuel.[7] In addition, VOCs are likely to be emitted from new manufacturing processes involving the plastics, chemical, and semiconductor industries, as well as older sources, such as dry-cleaning establishments and filling stations. PICs and VOCs are usually classified on the basis of their organic constituents. In addition to the multitude of individual compounds to be examined, problems arise from the lack of suitable chemical tracers or surrogates. For instance, total polycyclic aromatic compounds and benzo[a]pyrene, two commonly measured surrogates, might give but a poor re[illegible]tion of the carcinogenic potential of PIC mixtures under some conditions. A relative toxicity ranking of the components of complex mixtures produced by different combustion fuels and combustion conditions could be useful.

Important sources of PICs are wood, kerosene, and coal stoves; industrial and utility boilers; and internal-combustion engines.[43] Common sources of VOCs are household and commercial solvents, paints, dry-cleaning solvents, plastics manufacturing plants, unburned automotive fuel, and hazardous waste sites.[20,33,40,42] Hence, appropriate sites for exposure studies would include homes where solvents are regularly used indoors, homes near single major outdoor sources of PICs or VOCs or clusters of small industrial and commercial sources, and areas where PIC emission is dominated by one type of fuel used for space heating.

INDOOR POLLUTANTS: SPECIAL PROBLEMS AND PROSPECTS

Documentation of the importance of indoor concentrations of pollutants is profoundly altering air pollution epidemiology. Today in the United States over two-thirds of our time, on the average, is spent indoors. Therefore, the presence of even moderate amounts of pollutants indoors can influence the classification of a person with regard to pollutant exposure.

The increased energy costs of the 1970s stimulated efforts to conserve fuel through insulation, reduction in air exchange, and fuel switching. Residential and commercial buildings are a prime target for conservation efforts, because together they consume about one-third of this nation's energy, nearly all for heating, cooling, and moving air. Thus, reduction in ventilation or air exchange has become an important energy conservation strategy. But this strategy has tended to increase indoor concentrations of particles, CO, NO_2, radon, aldehydes, and other organic compounds. Some housing patterns may also increase concentrations of bacteria, fungal spores, and aeroallergens. In a related development, wood and coal stoves and kerosene heaters have displaced the more expensive oil, gas, and electricity in some areas. Many consumer products, furnishings, and construction materials recently introduced into the commercial market give off VOCs. Other older but unrecognized problems have come to the fore; asbestos in insulation and building materials and radon in soil and water are examples. (A more comprehensive treatment of this subject can be found in the 1981 National Research Council publication, Indoor Pollutants.[38])

Specific indoor exposures can now be considered in the framework described above for epidemiologic exposure assessment. Respirable particles, which were defined as those with median aerodynamic diameter less than 3.5 μm, were monitored in an extensive indoor air quality survey of over 80 homes in six U.S. cities;[44] 24-hour samples were collected every sixth day for up to 2 years from stationary samplers in each home. The results of this survey are illustrated in Figure 4. On the average, indoor concentrations were higher and had a much greater range across homes than outdoor concentrations. It is clear from comparisons of smoking and nonsmoking homes that smoking is a very important contributor to the increase in the respirable-particle fraction, which can also contain inert dust, fibers, aerosols (from spray cans), spores, aeroallergens, and viable organisms.

Several U.S. epidemiologic studies have reported that the percentage of young school-age children living with one or more smoking family members varied from 54% (in Tucson, Arizona) to 75% (in St. Louis, Missouri).[38] However, even in nonsmoking homes, indoor respirable-particle concentrations--due to a variety of unspecified

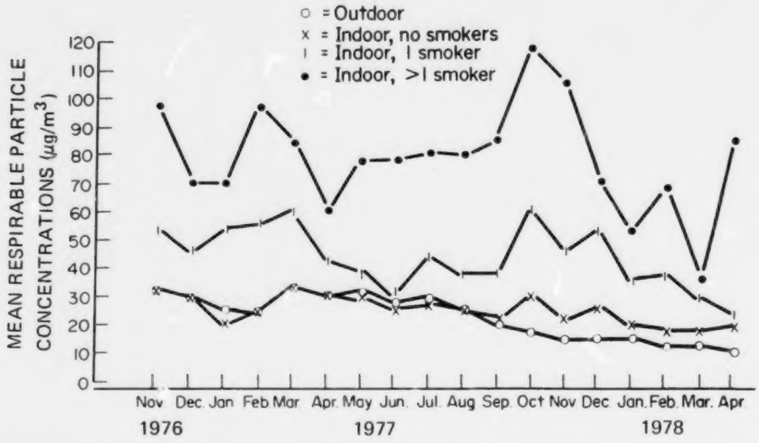


FIGURE 4 Monthly mean respirable-particle concentrations across six U.S. cities. Reprinted with permission from Spengler and Soczek.[45]

activities--can be higher than outdoor concentrations.[38] Thus, problems were encountered in attempting to investigate the health effects of these particles in ambient air, because the variation in indoor concentration among homes within cities is far greater than the variation in outdoor concentration between cities.

The impact of indoor pollutants on total exposure can also be illustrated with results of some recent personal-exposure studies. In the last 10 years, the availability of lightweight portable sampling pumps and diffusion badges has allowed investigators to compare total personal exposure to indoor and outdoor pollution simultaneously. These investigations have revealed low correlations between outdoor concentrations and integrated personal exposure for some important pollutants, such as respirable particles and NO_2. In the situations studied for these pollutants, indoor concentrations appear to be better predictors of time-averaged exposure (and the potential for substantial peak exposures) than outdoor concentrations. Preliminary results from EPA's Total Exposure Assessment Method (TEAM) study indicate that personal exposures to VOCs are greatly influenced by consumer product uses.

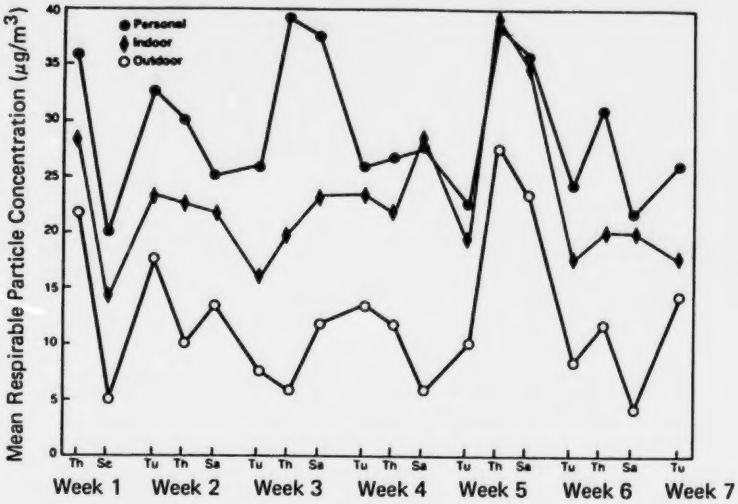


FIGURE 5 Daily average indoor, outdoor, and personal concentrations for 46 persons in Topeka, Kansas. Reprinted with permission from Spengler and Tosteson.[47]

In the personal-exposure studies on respirable particles, subjects (mostly adults) carried portable samplers and recorded time in various places and activities. The data were used to determine how accurately central-site outdoor monitors represented the actual day-to-day personal exposures within a community. In Topeka, Kansas, 45 nonsmoking adults carried monitors during the active 12-hour periods of the day.[54] Husband-and-wife teams participated in an 18-day study. Figure 5 illustrates the differences in daily outdoor, in-home, and personal concentrations of respirable particles collected in the study. Note that the indoor concentrations are higher than the outdoor, and the personal exposures higher still. This indicates that somewhere in their daily activities subjects were receiving a greater exposure to particles than could be explained by the measurements taken either in their homes or outdoors. Passive smoke exposure (either outside the home or in rooms other than those monitored) appeared to provide an explanation. In one set of measurements from this group, respirable particle concentrations were 20 $\mu g/m^3$ higher in those reporting some passive smoke exposure than in those reporting none. The personal exposures of neither the husband nor the wife were correlated with the ambient outdoor measurements. Husband and wife concentrations showed considerable common variance; their measurements had a correlation of 0.5. The wives' exposures were significantly correlated (0.7) with home measurements.

Although indoor concentrations do not completely explain personal exposures, information from the Kansas study and from other exposure studies[5] has indicated the importance of home measurements in understanding total personal exposure to particles. Categorical descriptor variables and ambient outdoor concentrations are notoriously poor predictors of personal exposures. Outdoor measures explain less than 1% of the interindividual variance in personal exposure to respirable particles. The indoor concentration by itself explains over 60% in adults.[45]

Similar studies have recently examined the role of various sources in determining total exposure to NO_2. Indoor residential concentrations correlated poorly with outdoor concentrations, but were related to frequency of gas cooking and variations in air exchange rates (including seasonal variations). In Portage, Wisconsin, where ambient NO_2 averages only 15 $\mu g/m^3$, gas cooking adds, on the average, 45 $\mu g/m^3$ to indoor concentrations.[41] Surprisingly, 3% of homes monitored in Portage, which has relatively clean air, exceeded the National Ambient Air Quality Standard of 100 $\mu g/m^3$. The important implication is that a substantial portion of the U.S. population, on an average day, is exposed to NO_2 at a concentration over the health standard, when both indoor and outdoor sources are considered together.

Epidemiologic research on indoor pollutants is only beginning. There have been very few systematic investigations of passive smoke exposure or exposure to aeroallergens, radon, and other common indoor contaminants. The relative contributions of these pollutants to the total indoor air quality problem remain to be determined.[44] Even the few reported studies have not adequately characterized exposures to indoor pollutants with direct measurements. The development of simple, lightweight, and inexpensive monitoring instruments will have great benefits in this field. Passive collectors that yield time-integrated measurements are useful, but are not always best for a particular application. Short-term peak concentrations, which can be measured only with continuous monitors, have greater biologic relevance for some pollutants.

SITING AND TIMING OF AIR POLLUTION MONITORS

In past epidemiologic studies, cost considerations and a simple view of exposure have favored the use of routinely collected data on air quality. Siting guidelines for EPA national air monitoring stations are available for primary pollutants (such as SO_2, nitrogen oxides, lead, and CO), secondary pollutants (such as O_3), and combinations of the two (PM_{10}). As noted earlier, the national network was not established for epidemiologic purposes. Although the data it provides might have been adequate for studies involving larger contrasts in exposure, many current studies must have tighter control over the error involved in estimating individual exposures via remote outdoor stations.

Decisions regarding the siting of stations for routine air monitoring were not usually made according to the needs of public health researchers. As a 1964 symposium on environmental measurements aptly noted:

> Some of the considerations in selecting a suitable (sampling) area were openness of the surroundings, availability of utilities, proximity to atypical sources, and approval of city building commission or other authorities.[57]

The later introduction of clean air standards promoted the location of monitors near emission sources in the most polluted areas of a given community, where violations would be most likely.

The search for ideal sampling locations for epidemiologic purposes has led to the use of complex statistical approaches to siting. A goal, for example, is a location that will represent a homogeneous population unit with regard to magnitude of exposure while minimizing the total number of stations. The complexity and expense of such efforts should not be underestimated. The Nashville air pollution study in the early 1960s, perhaps the most ambitious so far, used a regular grid of 123 monitoring stations.[64] Subareas with contrasting exposure could be identified, and some stations were determined to be redundant. It was feasible to identify such contrasts for only two pollutants, particles and SO_2. In spite of the wealth of data from the Nashville study, generalization to other cities, periods, and pollutants has been very difficult. Within cities, the potential variation in exposure over short distances and the nonuniform distribution of population frustrate statistical sampling strategies, which are limited by the availability of funds.

Rather than convert varied exposure to a homogeneous value, epidemiologic studies might need to take advantage of variability itself. Grid approaches to monitor siting appear to have less appeal today than approaches based on expert judgment. Locations for monitors in future studies will require information on meteorologic characteristics, sources and density of emission, and other conditions that indicate potential for accumulating high concentrations of pollutants. For example, a monitoring location suited for obtaining CO exposure estimates would not be appropriate for O_3, because direct automobile emission quenches atmospheric O_3.

Variations in pollutant concentrations over time are a major source of biologically relevant information about exposure. The nature of the questions asked by a particular epidemiologic study and the type of health effect under study dictate important decisions concerning sampling times and intervals. Pollutant concentrations vary substantially from year to year, season to season, and day to day, and from time to time in a given day. Temporal aspects of exposure are also involved in the process of reducing continuous data or sequential samples into single numbers. Theoretically, the ideal sampler would provide continuous measurements from which peaks, integrated exposures over different intervals, and trends might be discerned. But such a sampler would be prohibitively expensive, and it would not absolve researchers of the need to make sense of the limitless data produced.

The details of daily or even seasonal variation in pollutant concentrations would mean little in a study whose aim was to relate lifetime exposure with risk of chronic effects. Techniques for reconstructing past exposures and creating long-term historical exposure indexes are likely to be more appropriate in such instances.

Biologic models concerning the presumed action of air pollutants have not always been explicitly considered in planning epidemiologic studies. For some irritants, such as SO_2, the number and duration of peaks might be more relevant than smoothed average concentrations in determining effect. This applies to both chronic and acute effects, in that the role of cumulative acute insults in the development of chronic lung disease remains in question. Laboratory studies on animals and controlled-exposure studies on humans can provide guidance in determining relevant features of temporal variations.

CHARACTERIZATION STUDIES

Over the last 10 years, a number of studies have successfully characterized indoor and outdoor environments--for example:

- Houston Area Oxidants Study (HAOS).[4]
- Portland Aerosol Characterization Study (PACS).[61]
- Persistent Elevated Pollution Episodes (PEPE).[19]
- New York Summer Aerosol Study (NYSAS).[27]
- California Aerosol Characterization Experiment (ACHEX).[21]
- Regional Air Pollution Study (RAPS).[1]
- Denver Brown Cloud.[11]
- Sulfate Regional Experiment (SURE).[35]
- Harvard Air Pollution Health Study.[46]
- Total Exposure Assessment Method (TEAM).[59]
- New Jersey Project on Airborne Toxic Element and Organic Species (ATEOS).[30]

The characteristics of the exposed population and of the pollutants themselves were explored in some cases. These studies had a variety of objectives, but their results can be used to plan the characterization data needed for new epidemiologic studies. Lippmann *et al.*[32] used the design of PEPE, which characterized ambient air in regions near Indiana, Pennsylvania, to design a field study of children's response to regional haze at a summer camp. The Harvard Air Pollution Health Study included a number of characterization experiments that ultimately led to the identification and examination of population exposures to both indoor and outdoor pollutants. The ATEOS project has characterized urban areas with different mixes of industrial, commercial, and residential activities for the presence of potentially mutagenic or carcinogenic species;[30] it yielded information that can now be used in the design of epidemiologic studies on ambient carcinogens and mutagens.

The VOC studies conducted in the TEAM project have yielded important cross-sectional exposure information that suggests opportunities for future epidemiologic research.[59] Although this project measured a wide range of materials, future investigations must focus on specific questions, because there are a large number of potential compounds and sources. Characterization studies should eventually be able to limit the volatile organic hydrocarbons to an important subgroup that might require epidemiologic investigations. The TEAM study has shown that specific microenvironments (e.g., self-service filling stations) will have to be considered in future population studies and that we must include the characterization of populations that could be exposed to high concentrations in either indoor or outdoor environments.

Pollutant characterization for epidemiologic purposes must go beyond the standard indexes, which actually stand as surrogates for complex mixtures. The commonly used index TSP is an example. TSP is composed of particles of various sizes, primary and secondary pollutants, and inorganic and organic species. For instance, SO_4^{-2} species[53] and organic matter[12] are associated primarily with the fine-particle fraction (FP), whereas ammonium nitrate is usually found on both FP and coarse particles (aerodynamic diameter, greater than 2.5 µm).[26] Variations in the relative proportions of these components will affect the anticipated biologic effects of breathing air that contains them. Characterization of such components is essential in selecting study populations with critical contrasts in exposure.

A much improved kind of exposure assessment research, which will assist in the design of epidemiologic studies, is the resolution of sources that contribute to measured air concentrations. Most of the work to date has been done on the outdoor sources of particulate matter. Information on the approach called source-receptor modeling can be found in EPA reports and original research papers.[2, 13, 48] A variety of mathematical techniques are available, including chemical-element balance[17] and multiple-regression factor analysis.[25] The main product of each technique is an estimate of the percentage of particle mass in a given sample of air that can be attributed to an individual source or type of source. This information will be very useful in the development of measures to regulate the contributions of sources that are found to produce a health effect in an exposed population. It will also be helpful in explaining the variation in personal exposure within a sampled area that could be attributable to variation in individual proximity to sources.

EPA has recently published its rationale for converting the TSP standard to one based on PM_{10}, in recognition that not only the concentration of suspended particles but also particle size and site of deposition in the respiratory tract are important determinants of the risk of health effects.[55] In the future, it should be recognized that the potential health effects of inhaled particles also depend on the inherent toxicity or biologic activity of the particles, whether fine or coarse. For example, not all particles can be expected to be as toxic as alpha-quartz, a substance known to be highly toxic to the pulmonary alveolar macrophage (PAM) and to be highly fibrogenic.

Several groups have compared the ability of mineral dusts to kill cultured cells with their fibrogenicity in whole animals, to validate the ability of the in vitro cytotoxicity test to predict in vivo activity.[22, 23, 51] Recently, Hill and Hobbs compared the toxicity of several types of coal-combustion fly ash with that of a positive reference standard, DQ12 quartz. They found that the fly ash had little or no toxicity to PAM cells at concentrations up to 500 μg/ml of culture medium, although the quartz caused a large leak of enzymes from the cells at a concentration of 250 μg/ml.[22] Rats were then exposed by inhalation to the same two dusts, and the relative pulmonary toxicities of the dusts were evaluated by analysis of bronchoalveolar lavage (BAL) fluids. Although both dusts caused inflammation, as measured by neutrophil cell counts in BAL fluid, only the quartz increased the protein in BAL fluid, and the increase in enzymes in the fluid was much higher in the quartz-exposed than in the ash-exposed rats.[23] Thus, in this study the in vivo test validated the use of the PAM toxicity assay as a predictor of in vivo toxicity.

With the use of such end points as cell viability and release of enzymes, it can be suggested that the PAM cytotoxicity test can be used to rank the pulmonary toxicity of environmental dusts. Bioassays could play a very important role in prescreening a community in the design stages of an epidemiologic study. If incorporated into a study, bioassays might provide important clues for interpreting differences in responses (rates of illness or effects on pulmonary function) in the community.

Short-term biologic tests to determine exposure to harmful chemicals have been used most successfully to determine exposure to mutagenic-carcinogenic agents in high-risk populations. An example from air pollution research is the recent study of urinary mutagenic activity in children residing near a Montana smelter.[60] In contrast, with the notable exceptions of blood lead and carboxyhemoglobin measurements, there are no biologic methods for monitoring the extent of exposure of the general population to EPA criteria air pollutants. Such methods might be particularly difficult to develop for short-lived reactive pollutants that exert their effects in the lung. Biologic measures of oxidant exposure should therefore be sought in surrogate targets, such as red cells or serum proteins.[34]

When biochemical techniques have been developed much further, they might permit the precise measurement of biologically effective dose. However, measures of external exposure will still be important in determining relationships between environmentally monitored and internally absorbed concentrations of pollutants and will remain vital to epidemiology as long as such measures are the basis for regulation.

To assist in the characterization of a pollutant sample with respect to predicting the dose received by tissues, information on the effect of its physical and chemical matrix can be obtained. The nature of this matrix affects the bioavailability of inhaled chemical pollutants. The potential health effects of inhaled benzo[a]pyrene, for example, might depend on whether it is inhaled as a pure compound (a rare occurrence), inhaled after adsorption on particles, or inhaled as a component of a droplet of a complex organic mixture. The formulation affects the retention time of organic compounds in the lung.[49-52] Thus, knowledge of the amount of a specific type of chemical in the atmosphere is often no longer sufficient for predicting its health effects. As the ability to characterize pollutants improves, exposure assessment becomes an increasingly sophisticated tool for epidemiologic studies of air pollution.

REFERENCES

1. Allen, P.W. Regional Air Pollution Study: An overview. Preprint No.#73-21. Proceedings of the 66th Annual Meeting of the Air Pollution Control Association. Pittsburgh, Pa.: Air Pollution Control Association, 1973.

2. Anderson, M.K., E.T. Brookman, R.J. Londergan, J.G. Watson, and P.J. Lioy. Receptor Model Technical Series: Source Apportionment Techniques and Considerations in Combining Their Use. Vol. 5. Publication No. EPA/450/4-84/020. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1985. 191 pp. [Also available from the National Technical Information Service, Springfield, Va., as NTIS/PB85-111524.]

3. Annest, J.L., J.L. Pirkle, D. Makuc, J.W. Neese, D.D. Bayse, and M.G. Kovar. Chronological trend in blood lead between 1976 and 1980. N. Engl. J. Med. 308:1373-1377, 1983.

4. Beck, W.B., and G.K. Tannahill. An overview of the Houston area oxidant study. #78-30.1. Proceedings of the 71st Annual Meeting of the Air Pollution Control Association. Pittsburgh, Pa.: Air Pollution Control Association, 1978.

5. Binder, R.E., C.A. Mitchell, H.R. Hosein, and A. Bouhuys. Importance of the indoor environment in air pollution exposure. Arch. Environ. Health 31:277-279, 1976.

6. Bross, I. Misclassification in 2 x 2 tables. Biometrics 10:478-486, 1954.

7. Cannon, J.A. Air quality effects of residential wood combustion. J. Air Pollut. Control Assoc. 34:895-897, 1984.

8. Cleveland, W.S., B. Kleiner, J.E. McRae, and J.L. Warner. Photochemical air pollution: Transport from the New York City area into Connecticut and Massachusetts. Science 191:179-181, 1976.

9. Cobourn, W.G., and R.B. Husar. Diurnal and seasonal patterns of particulate sulfur and sulfuric acid in St. Louis, Missouri, July 1977-June 1978. Atmos. Environ. 16:1441-1450, 1982.

10. Copeland, K.T., H. Checkoway, A.J. McMichael, and R.H. Holbrook. Bias due to misclassification in the estimation of relative risk. Am. J. Epidemiol. 105:488-495, 1977.

11. Countess, R.J., G.T. Wolff, and S.H. Cadle. The Denver winter aerosol: A comprehensive chemical characterization. J. Air Pollut. Control Assoc. 31:1194-1200, 1981.

12. Daisey, J.M. Organic compounds in urban aerosols. Ann. N.Y. Acad. Sci. 338:50-69, 1980.

13. Dattner, S., and P. Hopke, Eds. Receptor Models Applied to Contemporary Pollution Problems. Pittsburgh, Pa.: Air Pollution Control Association, 1983. 368 pp.

14. Davis, D.L., and S. Gusman. Exposure assessment: Introduction. Toxic Subst. J. 4:4-11, 1982.

15. Electric Power Research Institute. Electric Power Research Institute/Gas Research Institute Workshop on Personal and Portable Monitoring Equipment, December 5-8, 1984. Palo Alto, Cal.: Electric Power Research Institute. (in press)

16. Frezieres, R.G., A.H. Coulson, R.M. Katz, R. Detels, S.C. Siegel, and G.S. Rachelefsky. Response of individuals with reactive airway disease to sulfates and other atmospheric pollutants. Ann. Allergy 48:156-165, 1982.

17. Friedlander, S.K. Chemical element balances and identification of air pollution sources. Environ. Sci. Technol. 7:235-240, 1973.

18. Gladen, B. and W.J. Rogan. Misclassification and the design of environmental studies. Am. J. Epidemiol. 109:607-616, 1979.

19. Hamilton, H.L., Jr., and S.N. Jones. Seminars/ Workshop Proceedings: Persistent Elevated Pollution Episodes (PEPE), March 1979. Publication No. EPA-600/9-81-016. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1979. 599 pp.

20. Harkov, R., B. Kebbekus, J.W. Bozzelli, P.J. Lioy, and J.M. Daisey. Comparisons of selected volatile organic compounds during the summer and winter at urban sites in New Jersey. Sci. Total Environ. 34:259-274, 1984.

21. Hidy, G.M., P.K. Mueller, D. Grogjean, B.R. Appel, and J. Wesolowski, Eds. The Character and Origins of Smog Aerosols: A Digest of Results from the California Aerosols Characterization Experiments. Vol. 10. Wiley-Interscience, 1980. 776 pp.

22. Hill, J.O., and C.H. Hobbs. Comparative cytotoxicity of DQ12-quartz and fly ash particles from coal combustion. Toxicol. Lett. 10:399-403, 1982.

23. Hobbs, C.H., R.L. Carpenter, D.E. Bice, J.L. Mauderly, J.A. Pickrell, S.A. Silbaugh, F.F. Hahn, R.F. Henderson, and R.K. Wolff. Comparative inhalation toxicity of fly ash from pulverized and fluidized bed combustion of coal, pp. 401-407. In M.B. Snipes, T.C. Marshall, and B.S. Martinez, Eds. Inhalation Toxicology Research Institute Annual Report, 1981-1982. Publication No. LMF-102, 1982. Albuquerque, N.M.: Inhalation Toxicology Research Institute.

24. Holland, D., and D. Mage. Carbon Monoxide Concentrations in Four U.S. Cities During the Winter of 1981. Publ. No. EPA 600/59-83-025. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1983. 75 pp.

25. Kleinman, M.T., B.S. Pasternack, M. Eisenbud, and T.J. Kneip. Identifying and estimating the relative importance of sources of airborne particulates. Environ. Sci. Technol. 14:62-65, 1980.

26. Kleinman, M.T., C. Tomczyk, B.P. Leaderer, and R.L. Tanner. Inorganic nitrogen compounds in New York City air. Ann. N.Y. Acad. Sci. 322:115-123, 1979.

27. Leaderer, B.P., D.M. Bernstein, J.M. Daisey, M.T. Kleinman, T.J. Kneip, E.O. Knutson, M. Lippmann, P.J. Lioy, K.A. Rahn, D. Sinclair, R.T. Tanner, and G.T. Wolff. Summary of the New York Summer Aerosol Study (NYSAS). J. Air Pollut. Control Assoc. 28:321-327, 1978.

28. Leaderer, B.P., R.T. Zagraniski, M. Berwick, and J.A.J. Stolwijk. Assessment of exposure to indoor air contaminants from combustion sources: Methodology and application. Am. J. Epidemiol., 1985. (in press)

29. Lioy, P.J. Ambient Measurements of Sulfate Species in the United States. Preprint #83-8.3. Proceedings of the 76th Annual Meeting of the Air Pollution Control Association. Pittsburgh, Pa.: Air Pollution Control Association, 1983.

30. Lioy, P.J., and J.M. Daisey, with T. Atherholt, J. Bozzelli, F. Darack, R. Fisher, A. Greenberg, R. Harkov, B. Kebbekus, T.J. Kneip, J. Louis, G. McGarrity, L. McGeorge,and N.M. Reiss. The New Jersey Project on Airborne Toxic Elements and Organic Substances (ATEOS): A summary of the 1981 summer and 1982 winter studies. J. Air Pollut. Control Assoc. 33: 649-657, 1983.

31. Lioy, P.J., and M.J. Lioy, Eds. Air Sampling Instruments for Evaluation of Atmospheric Contaminants. 6th ed. Cincinnati, Oh.: American Conference of Governmental and Industrial Hygienists, 1983. 600 pp.

32. Lippmann, M., P.J. Lioy, G. Liekauf, K.B. Green, D. Baxter, M. Morandi, B. Pasternak, D. Fife, and F.E. Speizer. Effects of ozone on the pulmonary function of children, pp. 423-446. In M.A. Melman, S.D. Lee, and M.G. Mustafa, Eds. Advances in Modern Environmental Toxicology. Vol. V. Princeton, N.J.: Princeton Scientific Publishers, 1983.

33. McMillin, C.R., L.B. Mote, and D.G. DeAngelis. Potential Atmospheric Carcinogens: Phase I. Identification and Classification. Publication No. EPA 600/2-80-015. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, 1980. 255 pp.

34. Morgan, D.L., A.F. Dorsey, and D.B. Menzel. Erythrocytes from ozone-exposed mice exhibit decreased deformability. Fund. Appl. Toxicol. 5:137-143, 1985.

35. Mueller, P.K., and G.M. Hidy. The Sulfate Regional Experiment: Report of Findings. Vols. 1-3. EPRI Publ. No. EA-1901. Palo Alto, Cal.: Electric Power Research Institute, 1983.

36. National Council on Radiation Protection and Measurements. Exposures from the Uranium Series with Emphasis on Radon and Its Daughters. NCRP Report No. 77. Bethesda, Md.: National Council on Radiation Protection and Measurements, 1984.

37. National Research Council, Committee on Indoor Pollutants. Indoor Pollutants, pp. 307-322. Washington, D.C.: National Academy Press, 1981.

38. National Research Council, Committee on Indoor Pollutants. Indoor Pollutants. Washington, D.C.: National Academy Press, 1981. 537 pp.

39. National Research Council, Committee on Medical and Biologic Effects of Environmental Pollutants. Ozone and Other Photochemical Oxidants. Washington, D.C.: National Academy of Sciences, 1977. 719 pp.

40. National Research Council, Committee on Vapor-Phase Organics from Diesels. Vapor-Phase Organic Pollutants: Volatile Hydrocarbons and Oxidation Products. Washington, D.C.: National Academy Press, 1976. 411 pp.

31. Quackenboss, J.J., M.S. Kanarek, J.D. Spengler, and R. Letz. Personal monitoring for nitrogen dioxide exposure: Methodological considerations for a community study. Environ. Int. 8:249-258, 1982.

42. Singh, H.B., L.J. Salas, A.J. Smith, and H. Shigeishi. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. 15:601-612, 1981.

43. Smith, K.R., A.L. Aggarwal, and R.M. Dave. Air pollution and rural biomass fuels in developing countries: A pilot village study in India and implications for research and policy. Atmos. Environ. 17:2343-2361, 1983.

44. Spengler, J.D., D.W. Dockery, W.A. Turner, J.M. Wolfson, and B.G. Ferris, Jr. Long-term measurements of respirable sulfates and particles inside and outside homes. Atmos. Environ. 15:23-30, 1981.

45. Spengler, J.D., and M.L. Soczek. Evidence for improved ambient air quality and the need for personal exposure research. Environ. Sci. Technol. 18:268A-280A, 1984.

46. Spengler, J.D., and G.D. Thurston. Mass and elemental composition of fine and coarse particles in six U.S. cities. J. Air Pollut. Control Assoc. 33:1162-1171, 1983.

47. Spengler, J.D., and T.D. Tosteson. Personal Exposure to Respirable Particles. Presented at Environmetrics '81, Conference of the Society for Industrial and Applied Mathematics, Alexandria, Va. April 8-10, 1981.

48. Stevens, R.K. and T.G. Pace. Overview of the Mathematical and Empirical Receptor Models Workshop (Quail Roost-II). Atmos. Environ. 18:1499-1506, 1984.

49. Sun, J.D. and R.O. McClellan. Respiratory tract clearance of ^{14}C-labeled diesel exhaust compounds associated with diesel particles or as a particle-free extract. Fund. Appl. Toxicol. 4:388-393, 1984.

50. Sun, J.D., R.K. Wolff, H.M. Aberman, and R.O. McClellan. Inhalation of 1-nitropyrene associated with ultrafine insoluble particles or as a pure aerosol: A comparison of deposition and biological fate. Toxicol. Appl. Pharmacol. 69:185-198, 1983.

51. Sun, J.D., R.K. Wolff, G.M. Kanapilly, and R.O. McClellan. Effect of particle association on the biological fate of inhaled organic pollutants, pp. 1137-1151. In M.W. Cooke and A.J. Dennis, Eds. Polynuclear Aromatic Hydrocarbons. Vol. 7. Columbus, Oh.: Battelle Press, 1982.

52. Sun, J.D., R.K. Wolff, G.M. Kanapilly, and R.O. McClellan. Lung retention and metabolic fate of inhaled benzo(a)pyrene associated with diesel exhaust particles. Toxicol. Appl. Pharmacol. 73:48-59, 1984.

53. Tanner, R.L., R. Garber, W. Marlow, B.P. Leaderer, B.P., and M.A. Leyko. Chemical composition of sulfate as a function of particle size in New York summer aerosol. Ann. N.Y. Acad. Sci. 322:99-113, 1979.

54. Tosteson, T., J.D. Spengler, and R.A. Weker. Aluminum, iron, and lead content of respirable particulate samples from a personal monitoring study. Environ. Int. 2:265-268, 1982.

55. U.S. Federal Register. Proposed Revisions to the National Ambient Air Quality Standard for Particulate Matter. March 20, 1984. Vol. 49, No.5, pp. FR 10408-10462.

56. U.S. National Institute of Environmental Health Sciences. Biochemical and cellular markers of chemical exposure and preclinical indicators of disease. In Human Health and the Environment: Some Research Needs. Research Triangle Park, N.C.: U.S. National Institute of Environmental Health Sciences, 1985. (in press)

57. U.S. Public Health Service. Symposium: Environmental Measurements: Valid Data and Logical Interpretation, pp. 109-110. Public Health Service Publ. No. 999-AP-15. Washington, D.C.: U.S. Department of Health, Education, and Welfare, Public Health Service, 1964.

58. Utell, M.J., P.E. Morrow, and R.W. Hyde. Airway reactivity to sulfate acid aerosols in normal and asthmatic subjects. J. Air Pollut. Control Assoc. 34:931-935, 1984.

59. Wallace, L.A., E.D. Pellizzari, T.D. Hartwell, C. Sparacino, and H. Zelon. Personal exposure of volatile organics and other compounds indoors and outdoors: The TEAM Study. Preprint #83-9.12. Proceedings of the 76th Annual Meeting of the Air Pollution Control Association. Pittsburgh, Pa.: Air Pollution Control Association, 1983.

60. Warren, G.R., and S.J. Rodgers. Urine mutagen screening as a population monitoring technique: Children in an isolated, high lung cancer mortality area, pp. 39-48. In B.A. Bridges and B.E. Butterworth, Eds. Indicators of Genotoxic Exposure. Banbury 13. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratories, 1982.

61. Watson, J.G. Chemical Element Balance Receptor Model Methodology for Assessing the Source of Fine and Total Suspended Particulate Matter in Portland, Oregon. Ph.D. Dissertation, Oregon Graduate Center, February 1979. 525 pp.

62. Wilson, R., J.D. Spengler, S. Colome, and D. Wilson. Health Effects of Fossil Fuel Burning: Assessment and Mitigation. New York: Ballinger Publishing Co., 1980. 416 pp.

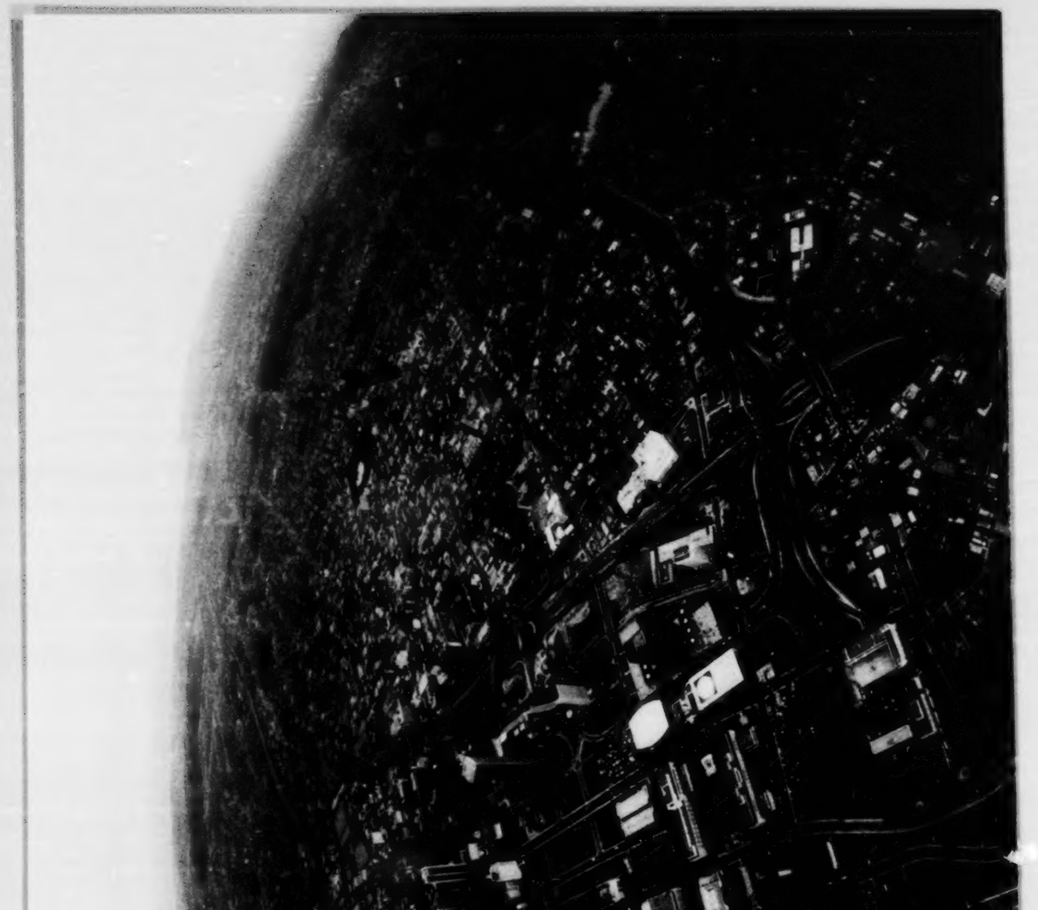
63. Wolff, G.T., and P.J. Lioy. Development of an ozone river associated with synoptic scale episodes in the eastern United States. Environ. Sci. Technol. 14:1257-1261, 1980.

64. Zeidberg, L.P., J.J. Schuenem, R.A. Prendle, and P.A. Humphrey. Air pollution and health: General description of a study in Nashville, Tennessee. J. Air Pollut. Control. Assoc. 11:289-297, 1961.

65. Ziskind, R.A., K. Fite, and D.T. Mage. Pilot field study: Carbon monoxide exposure monitoring in the general population. Environ. Int. 8:283-293, 1982.

Chapter 4

Concepts and Strategies in Planning Epidemiologic Studies on Air Pollution



4

CONCEPTS AND STRATEGIES IN PLANNING EPIDEMIOLOGIC STUDIES ON AIR POLLUTION

INTRODUCTION

This chapter addresses the principles that underlie the epidemiologic approach to air pollution research. Because ambient air pollution is generally less severe than in previous years, it is harder than it once was to detect most adverse health effects of pollution with a high degree of certainty. Research strategies that used to be demonstrably successful need further development and refinement if they are to be equally successful in solving the major research problems that remain. Initial success in protecting the public from the effects of air pollution has led to a situation in which the research questions must be more precise and the strategies chosen to address them more focused. The need for precision makes it necessary to seek out appropriately sensitive research tools and methods that will be capable of linking today's exposure with today's and tomorrow's health effects.

This discussion of research strategies for the epidemiologic study of air pollution is guided by several principles. First, the development of research strategies and the specification of research questions must precede the creation of specific study protocols. Second, epidemiology should be part of a larger framework in which epidemiologic, toxicologic, and clinical studies inform, complement, and reinforce each other. Third, epidemiologic studies of air pollution should be highly sensitive to small risks of disease, because large numbers of people are exposed; to provide credible estimates of those risks, they will require careful attention to all potential sources of error at every phase of their design and conduct. Fourth, the multifaceted nature of most air pollution problems requires that planning in epidemiology be interdisciplinary, involving collaboration between different scientific disciplines and between research sponsors and investigators. Fifth, the link between epidemiology and regulation will be a two-way street, with research planning illuminated by a clear understanding of the practical issues and constraints involved in regulation, and the regulatory process influenced by the product and capabilities of research.

COMMUNICATION OF EPIDEMIOLOGY WITH OTHER RESEARCH DISCIPLINES

Optimal use of the epidemiologic approach requires that it communicate with the parallel disciplines of clinical research and animal toxicology. This is distinct from the development of multidisciplinary research teams. Communication between scientists in the separate disciplines is essential and should not be limited to scientists who are perceived to be working on the same research questions. This communication can always benefit from administrative sponsorship and encouragement, including attention to such mundane matters as attendance at conferences, the locations of offices and laboratories, and participation in strategic planning of research and development of individual research projects.

Interdisciplinary contact will improve any epidemiologic strategy in air pollution in at least three ways. First, results of experiments in the laboratory and clinic will generate useful hypotheses for epidemiologic studies. Examples are the observation of cellular, whole-animal, or human adaptational responses to irritants as a basis for studying the responses of various groups to short-term pollution episodes and the observation of a synergistic effect of two pollutants as a basis for selecting communities potentially at high risk. Second, clinical research and toxicology are needed to provide better epidemiologic research tools. The development and validation of short-term biologic markers that reflect long-term respiratory damage constitute a good example. Laboratory investigators concentrating on disease mechanisms or therapy are often unaware of the potential applications of their work in population studies. For instance, a diagnostic test that is considered to be superfluous or too inaccurate for clinical work might be highly appropriate for testing large populations, because of its low cost and noninvasive nature. Research and development activity that leads to new research tools for epidemiology should be distinguished from empirical research on disease mechanisms and perhaps require separate administration and funding. Third, as discussed below, evidence from clinical research and toxicology is used by epidemiologists to strengthen the inference of causality in observed relationships between air pollution and health effects.

Epidemiologic activity also contributes to clinical research and toxicology. It can be an excellent source of hypotheses for laboratory studies and, more important, provide an outlook on disease that is critical for setting priorities. Apart from its ability to produce data and answer specific research questions, epidemiology offers a perspective and a set of concepts that can be used to guide efforts in disease prevention and research design.

CONSTRUCTING APPROPRIATE RESEARCH QUESTIONS

"The epidemiological method is the only way of asking some questions in medicine, one way of asking others, and no way at all to ask many."[16]

Research planners can reduce the chances of investing in inappropriate or inconclusive studies by clearly identifying research questions in advance. We refer here to a research question as a broad statement of a problem, rather than a specific epidemiologic hypothesis for an individual study. Major air pollution research questions seldom emerge ab initio from the intellects of creative scientists. Most are public health questions that are developed through interplay of the interests and capabilities of the scientific community with extrascientific forces, such as the availability of research funds and the regulatory process. Once a question has been articulated and is determined to be important from the standpoint of public health, research planners have the goal and responsibility of finding the most productive investigative strategy or determining that epidemiologic studies are not feasible. In practice, an iterative process is used both to develop and refine the formulation of research questions and to match each formulation with the optimal strategy. The cycle of marshaling facts to make a question explicit, devising a strategy, and then refining the question with new facts is parallel to the cycle of hypothesis-test-hypothesis that takes place at the level of individual studies. In this type of applied research, the development and refinement of the question and of the strategy are inseparable, and the investigator contributes equally to both.

The importance of specifying research questions cannot be overemphasized. As in all scientific disciplines, epidemiologic research questions begin in a rather general form and are pruned to testable hypotheses that form the basis for design of individual studies. Every epidemiologic study of the adverse health effects of air pollution has to be crafted around the pollutant in question and the adverse effect under consideration. The characteristics of the population at risk, the time between exposure and effect, and the amounts of exposure needed to produce an effect of a given magnitude are specified to some degree in the formulation of a study hypothesis. These elements of a hypothesis usually cannot be specified to the last detail; but, for a hypothesis to be useful, some specification of each element must at least be implied.

Each study must conform to various investigative constraints. These constraints, which must be appreciated early in planning, are imposed by such factors as:

- The frequency and natural history of the disease.
- The rate and the extent to which exposure to the pollutant in question changes over time.
- The availability of biologic markers of exposure or early effect.
- Other known or suspected causes of the health effects in question.

The overall research strategy has to be chosen with the best possible understanding of these four separate dimensions, and the detailed research protocol has to be designed to take them fully into account. The more we recognize that exposures to pollutants change and that given diseases have various causes, the more challenging it becomes to design a penetrating and efficient epidemiologic research protocol. Protocols are most penetrating and rewarding when the detailed research plan focuses on a single answerable hypothesis. The few exceptions to this important general rule include broad epidemiologic surveys designed explicitly for surveillance and the development of new hypotheses.

Epidemiology can be used to produce several different kinds of information about air pollution and health. The kind of information sought depends on the goals of the researcher. The remainder of this section discusses six types of broad research questions that can be addressed epidemiologiclly and briefly describes the capabilities of epidemiology to answer each type (for a more complete discussion of these issues, see, for example, Morris's Uses of Epidemiology[16]):

1. How does the state of health of a particular community with respect to disease Y compare with that of other communities? With itself over time?

2. What is the natural history of disease Y? Its clinical spectrum? How does it progress?

3. Is there any association between exposure X and disease Y? Is the association causal?

4. How much does the risk of disease increase as exposure increases (dose-response relation)? Is there a magnitude of exposure for which the disease risk is zero (a threshold)?

5. What are the risks of disease among various groups in the general population?

6. How much of disease Y is due to exposure X? How much will be prevented if exposure is reduced?

Question 1, regarding the monitoring of the health of a population, can be addressed only with epidemiologic methods. The relation of this question to air pollution concerns is indirect, however, except for its role in identifying study populations on the basis of contrasting disease patterns. Question 2, about the pathogenesis and natural history of a disease, can be answered through clinical observation and through epidemiology; but this type of question is rarely at the center of interest in air pollution studies, because there appear to be no unique "air pollution diseases." Moreover, although epidemiology can undoubtedly contribute to the understanding of how an exposure results in disease, detailed information of this kind is normally best provided by intensive clinical and laboratory studies.

Most applications of epidemiology in air pollution research have been to answer questions about correlations and causal relationships between air pollutants and various human health effects--Questions 3, 4, and 5. To address them, the epidemiologist normally uses the measure known as relative risk, the ratio of the incidence or prevalence of an adverse effect in one population to the incidence or prevalence in another population with a different degree of exposure.

Epidemiology can be very effective in answering Question 3, about the existence of any association between air pollutants and disease, particularly if the relative risk involved is large (sometimes arbitrarily defined as 3.0 or greater).[14] In such a situation, it is usually most sensible to compare populations at highest exposure with those whose exposures are low or nil. If the relative risk is extremely large and the disease is relatively rare in nonexposed persons, the association will often be noticed first by clinical observation, as in the case of the relationship between vinyl chloride and angiosarcoma of the liver or between asbestos and mesothelioma. It is reasonable to presume that, in most populations without extreme exposure, relative risks of overt clinical disease associated with air pollution are of low to moderate magnitude (approximately 1.2-3.0). Detection and accurate quantification of effects of this magnitude present the greatest methodologic challenges to contemporary epidemiology. Nevertheless, because it is unethical to conduct studies involving deliberate long-term exposures or acute exposures that might produce irreversible effects, epidemiologic studies will remain the only way to detect pollution-related forms of common chronic or serious acute diseases in humans.

Epidemiologic studies of air pollution have much greater limits in providing finely tuned information about dose-response relationships or about thresholds or "safe levels" (Question 4), particularly when small relative risks of chronic diseases are produced by years of low-dosage exposure. In those situations, it is extremely difficult to discriminate, with the necessary degree of precision, among populations with relatively minor differences in exposure, for instance, long-term exposure to ozone at 0.08 ppm versus 0.12 ppm. In addition, if the amounts of individual pollutants are highly correlated and tend to rise and fall together from time to time and place to place, the role of each pollutant can be difficult to isolate. Larger exposures can be studied to construct models that simulate the behavior of pollutants at lower dosages, but the reliability of mathematical extrapolation is limited by its dependence on unavoidable and untestable assumptions about the dose-response relationships. Future studies will gradually become better at providing quantitative information about the relationships between air pollutants and health, if the techniques for assessing exposure and effect mentioned in this report are developed and if research planning is appropriate.

Epidemiology, the basic science of preventive medicine and public health, views disease at the population level, but it can be used to predict the risks of disease in individuals or groups with various characteristics of interest (Question 5). By virtue of the mandate of the Clean Air Act (if for no other reason), it is essential to understand the range of susceptibility to air-pollution-related disease in the general population. Except in a few instances of controlled-exposure studies of volunteers with defined characteristics, such as pre-existing illness, epidemiology is necessary to identify high-risk groups. But precise determination of dose-response relations for each sensitive group is generally not feasible today.

The epidemiologic approach is uniquely suited to answer Question 6, although it seems to have been asked only rarely in relation to air pollution. This type of question, which deals with attributable risk rather than relative risk, asks how much of the overall burden of disease in a population is attributable to air pollution over the entire range of exposure. The answer has obvious and important public health implications, because it indicates the total amount of disease that is potentially preventable and the amount that would not occur if air pollution were reduced. Results of research to answer this kind of question are useful in making decisions about reducing exposures across the board, regardless of local or individual variations in susceptibility or risk and regardless of the relative importance of direct effects and synergistic effects, which are more difficult to know ahead of time. Epidemiology offers a direct means for predicting and later assessing the public health impact of changes in the environment, whether positive or negative, deliberate or unintentional.

In summary, Questions 1 and 2 are fundamentally epidemiologic, but are likely to be of limited interest in EPA's air pollution activities; epidemiology has made and can continue to make substantial contributions toward answering Questions 3 and 5 and, to a smaller extent, Question 4; and the epidemiologic approach has scarcely been applied to Question 6, although that application might be valuable.

CONSIDERATIONS IN STUDY DESIGN, ANALYSIS, AND INTERPRETATION

Epidemiologic projects concerning air pollution are among the most difficult to design. One reason is that ambient air pollution adds small increments to the respiratory morbidity risks of large masses of people, rather than large increments to the risks of a few. The dynamic and complex nature of air pollution makes it particularly difficult to measure, and its very nature surrounds it with confounding factors, such as temperature and humidity. Study design thus affords little margin--yet frequent opportunities--for error. Furthermore, epidemiologic studies, unlike laboratory experiments, are not easily repeated, so elimination of potential errors during study design is of paramount importance. Evaluation of all potential errors (such as that caused by the combination of very low exposure and low risk of effect) might lead study planners to conclude that epidemiologic studies are not feasible for providing the particular information desired.

The design of each study is a multistage process that begins with the extraction of a specific hypothesis from a general research question and ends with detailed budget estimates. In between, the designers must decide what exposure and what outcome are most pertinent and which measurements of each to use. They must then identify potential confounding variables, choose a study method and study populations that accommodate the hypothesis, and plan for the eventual analysis and interpretation of the data. This by no means involves a rigid sequence; the order of the steps varies, and often a decision about one step contains or implies decisions about others. Nonetheless, each step plays a distinct role in the study's integrity and the certainty that can be attached to its results.

The overall goal is to design studies so as to increase their validity in detecting and estimating the magnitude of the relationships between air pollution and health. Validity has two components: sensitivity and specificity. Sensitive studies have a low probability of labeling a harmful situation as harmless, and specific studies have a low probability of labeling a harmless situation as harmful. Ideal studies are sensitive enough to detect small but widespread effects, yet specific enough to discriminate real from spurious effects.

The complexity of the relationships among all the variables that could affect results of air pollution studies has two important implications:

- Study design and planning require expertise regarding the concepts of epidemiologic research design.

- The success or failure of future studies will depend increasingly on how well exposure, effect, and confounding variables have been characterized during study planning.

Study designers must have as much prior information as possible concerning the distribution of the factors responsible for nonrandom errors and confounding in the various populations being considered for study. The information can be inferred from previous studies of similar populations or obtained directly from the study populations themselves either before or during the study in question. If the information is obtained during planning, it can be used to alter the design of the study, change sample sizes, or influence the selection of study populations. Random errors (and nonrandom errors that behave as random ones in populations) can be mitigated by increasing sample size. Thus, epidemiology can sometimes take advantage of such data as those on death certificates, which individually are unreliable, but which yield reliable estimates of group characteristics when used in large numbers. In contrast, errors due to confounding or uneven biases cannot be corrected by increasing sample size, and other strategies must be used.

It is not within the scope of this report to discuss all the complex design considerations involved in weighing and managing potential sources of error. Once data have been collected, errors in analysis or interpretation can contribute to the total burden of error (and hence validity) of an epidemiologic study of air pollution. A few pitfalls are particularly likely in air pollution studies, but they can be avoided if anticipated during planning. This subject is at the heart of epidemiologic training and is treated in detail in textbooks and courses on research methodology. A few relevant concepts are introduced in Appendix C to point out the particular challenges for air pollution studies.

AVAILABLE METHODS FOR EPIDEMIOLOGIC STUDIES

Epidemiology depends on a small number of distinct study methods, any of which can be applied to air pollution questions.

DESCRIPTIVE EPIDEMIOLOGY OR "UNIVARIATE" STUDIES

The simplest form of epidemiologic study merely examines the frequency or severity of a disease or of a risk factor by personal characteristics, time, or place. This kind of study is referred to as descriptive or univariate, because it covers either exposure or effect, but not both. Descriptive epidemiology can be very helpful in identifying nonrandom variations in the occurrence of disease or exposure that can lead to study hypotheses.

Data on the geographic distribution of exposure to air pollution or of putative effects can help in the planning of research strategies. Maps of nationwide emission of various pollutants exist, and similar maps of air monitoring-station results should also be made available, with recognition of the limits of the data. The National Cancer Institute has published mortality maps by standard economic areas in the United States for nonmalignant respiratory diseases.[13] Data on geographic variations in respiratory morbidity, which would be even more valuable, are not available in the United States, and their development is hampered by lack of consistency in reporting or coding of morbidity events. In some instances, it might be helpful to know geographic variations in hypersusceptibility factors, such as asthma and α_1-antiprotease deficiency.

ECOLOGIC STUDIES

In ecologic studies, the group, rather than the individual, is the unit of comparison. Aggregate information is used, instead of individual data, on both exposure and effect. Studies that use aggregate data on exposure and individual data on health effects can be considered "semiecologic" studies. Inferences based on ecologic studies tend to be much weaker, and there is a much greater loss of information than when individual data are used. Ecologic studies can involve comparison of exposure and disease rates over time in the same population (temporal studies) or comparisons of exposure and disease rates in various geographic areas at the same time (geographic studies).

Ecologic studies are often attractive because of their relatively low cost, straightforward and rapid completion, and relative insensitivity to demands for data. They have some serious weaknesses, however. Confounding can be a severe problem, owing to the difficulty of obtaining comparable and reliable data for whole populations on such factors as smoking. There are also problems with respect to a wide variety of data elements, including exposure magnitude, disease rates, population characteristics, and migration in and out of the areas studied. Conclusions regarding individual risk must be drawn cautiously, because data on individual behavior that can influence risk are not collected. Recent articles provide a more complete discussion of the problems associated with this method.[15]

When the required data are of adequate quality, ecologic studies have a role in an air pollution research program. Comparisons of disease rates between populations help us to understand the potentially preventable fraction of total disease burden, to target high-risk populations for study, and to avoid studies in populations whose exposure or disease rate is too uniform.

COHORT METHOD

The cohort, or "prospective," method can be based on records of exposure and effect that are concurrent or historical (in which case the cohorts are defined by historical information and followup time has already elapsed). This design is usually not suitable for rare diseases, because the sample size must be too large, but it can be excellent for common diseases. The exposed cohort is compared with a cohort or cohorts with smaller or no exposure, and disease or other adverse-effect rates are ascertained during a followup period. The differences are presumed due to the exposures, if confounding can be handled and the populations appear comparable in respects other than the exposure of interest. This method is useful for investigating the effects of long-term exposures and for diseases that have long latent periods. Its advantages include the possibility of looking at many different diseases in the cohorts simultaneously with little increase in cost and the ability to estimate incidence rates, as well as relative risks.

Historical cohort studies, commonly used to study occupational exposures, have been used only rarely to study exposures to air pollution. They require identification of subjects on the basis of existing records, reconstruction of individual exposure histories, and tracing of subjects toward the present for key health events. Although workplaces have sometimes routinely collected data that allow reconstruction of exposure, few such data exist for community exposure to air pollutants. Techniques for reconstructing pollution exposure, perhaps based on residential histories, remain to be developed. Such techniques would also be of use in case-control studies. The accuracy of such historical estimates is likely to be relatively poor.

Truly prospective longitudinal studies, based on individual measurements of exposure and effect, are likely to provide the strongest basis for epidemiologic inference on air pollution, because they give the investigator the greatest degree of control over random and nonrandom errors. But they are sometimes prohibitively expensive. Moreover, it might take years of observation for the outcome of interest to occur in a statistically significant number of subjects. Where responsibility for public health is involved, avoidable delays in collecting pertinent information about air pollution cannot be justified. Apart from ethics, short-term studies (5 years or less) have practical advantages over long-term studies, including more complete followup of subjects, better control of selection bias among subjects who remain in the study, and greater stability of research teams.

Longitudinal studies often require a tradeoff between sample size and duration of followup. An investigator might achieve the same certainty about an association between an air pollutant and an effect by studying, for example, 50 people for 8 years and by studying 1,000 people for 2 years. The statistical-power relationships involved in longitudinal measurements of lung function in groups of various sizes for various periods have been analyzed recently by Berry (see Table 1, in Chapter 5).[2] The cost and information value of these options must be explored in the planning of longitudinal studies.

Shorter durations of study tend to mitigate perhaps the largest problem of prospective studies of chronic air pollution effects--loss of subjects to followup because they change residences. In the UCLA study of chronic respiratory effects in two areas of Los Angeles, 54% and 45% of the subjects from the lower- and higher-exposure areas, respectively, were lost to followup after 5 years, owing largely to residential mobility.[24] The serious adverse impact of mobility on the power of epidemiologic studies of chronic disease (regardless of the method used) has been discussed elsewhere.[20]

Another kind of tradeoff--between precision of exposure assessment and statistical precision or power--is related directly to the design of cohort studies. Small cohorts allow more opportunities to obtain precise exposure and effect data; large cohorts, although they usually involve less precise data, provide greater statistical sensitivity and are easier to generalize to unstudied populations. The small-cohort and large-cohort approaches are therefore distinct and can be used to address different kinds of questions. Their use in strategies pertaining to current questions is illustrated in Chapter 5.

Many chronic disease epidemiologists are working to develop research strategies and tools for the short-term study of the causes and modifiers of long-term conditions. Some of their efforts have focused on short-term biologic markers and the identification of susceptible groups. Valid measurement of early disease might allow studies of chronic lung disease to be completed, for example, in 3-5 years, rather than 15-20 years. Chapter 2 pointed to rapid decline in lung function as a useful physiologic indicator that permits compression of longitudinal studies. Early disease markers might also provide outcome measures that are more frequent than overt disease and thus magnify relative risk and increase the statistical power of cohort studies.

The success of the Framingham and Tecumseh studies has led to widespread appreciation of the value of longitudinal cohort studies in identifying biologic and lifestyle measurements that predict disease in groups. Several epidemiologists are using data from these and similar longitudinal studies to identify the conditions under which short-term cohort studies might provide the same information as long-term ones.

NESTED CASE-CONTROL METHOD

A combination of the cohort and case-control approaches, known as the "nested case-control" or "case-control-within-a-cohort" study, has recently come into wider use, because it can lead to lower costs and more reliable results. In this method, a large cohort is followed, historically or prospectively, and outcomes are determined for all (e.g., whether a subject died of cancer), but some exposure data (such as results of tests on stored blood samples) are measured or coded only for a subset of subjects who develop a health effect of interest (cases) and a random subset of subjects who do not (controls). Because the statistical value of having more than about three controls per case is usually negligible, and because most chronic diseases have relatively low incidences, even in high-risk groups, savings can be large. The nested case-control method can capitalize on situations in which blood or other biologic samples have been obtained and set aside for storage as part of a baseline or periodic evaluation of a cohort.[27] Therefore, this approach should permit the wider use of biologic markers in population studies when the cost of each marker assay is a barrier.

CROSS-SECTIONAL STUDIES

Cross-sectional studies can be considered to make up a subtype of the cohort study, in that subjects are enrolled according to extent of exposure. In cross-sectional studies, exposure and effect data are collected concurrently, and that permits more rapid completion of studies and lower total costs. The chief disadvantages are that information about past exposure is often unreliable or unavailable and migration into and out of the geographic areas in the study (particularly of especially healthy or especially unhealthy people) might bias the sample. In addition, because exposures and effects are measured concurrently, it is difficult to ensure that exposures preceded the effects.

Some studies have suggested that one-time cross-sectional evaluations of adverse health effects, such as lung function deficits and respiratory symptoms, are less sensitive than longitudinal evaluations of changes over time. Cross-sectional study of adults in Berlin, New Hampshire, in 1962 showed no greater prevalence of symptoms in those residing in more polluted areas; however, a followup study in 1967 indicated that improvements in air quality had led to detectable improvements in symptom prevalence.[6] Studies by Van Der Lende in the Netherlands have suggested that longitudinal measurement of lung function is a more sensitive indicator of air pollution effects than cross-sectional measurement.[25] In fact, there are puzzling discrepancies in the normal relationship between age and lung function, depending on whether curves are obtained by cross-sectional or by longitudinal methods.[7] The choice between cross-sectional and longitudinal approaches is affected to some degree by the difference between the fluctuation in exposures or effects from person to person and the fluctuation from time to time for the same person. When data on individuals are unstable, compared with inherent variability between persons, there might be little advantage in studying the same person repeatedly.

Longitudinal (cohort and case-control) studies have substantial advantages in drawing inferences of cause and effect; but, if an investigator is sensitive to the vulnerable aspects of the cross-sectional method and plans accordingly, sound studies are possible for some research questions, particularly for short-term exposures and acute effects. The migration problem can be addressed by restricting the study to long-term community residents or at least analyzing their results separately. This solution is not perfect, because the long-term residents might differ from others in responses to air pollutants. Furthermore, potential errors in assessing long-term past exposure seriously limit the ability of the cross-sectional approach to provide precise information on dose-response relations for chronic effects. However, even for chronic effects, the cross-sectional method can be used to infer magnitude of risk when cause-effect relations are already known, to develop important new hypotheses for further study by other means, and to check and confirm, in a range of settings, a relationship found in a longitudinal study.

CASE-CONTROL METHOD

In the case-control method, one starts by defining persons who do (cases) or do not (controls) have the outcome (usually a disease) of interest and looks into their history for evidence of exposures. The problems lie in defining the disease, measuring past exposures reliably, selecting the control group, and handling confounders in the analysis. The prevalence of exposure to a suspected agent is the important determinant of sample size and hence study sensitivity, but rarity of the disease is usually not a hindrance in this approach if enough cases can be found, even if from multiple sources. In fact, a case-control study is sometimes the only feasible kind for investigating rare diseases. It permits a variety of exposures to be examined at relatively low cost--a clear advantage over cohort methods. In contrast with cohort approaches, one cannot ordinarily study more than one disease at a time without substantial increases in total sample size to ensure that each outcome is adequately represented.

Case-control studies on the effects of ambient air pollution have been infrequent, perhaps because of the difficulty of reconstructing past exposures with acceptable precision. Also, cases and controls can differ in their recall of types and magnitudes of air pollution; data can sometimes be strengthened by direct validation of past exposure, and biologic markers of exposure might become valuable in this regard. In contrast, effect or outcome data can be scrupulously defined, with hospital or pathology records if necessary. Because the chief instrument in a case-control study is a questionnaire, it is comparatively easy to obtain information about the wide range of potential confounders that plague air pollution research. Important summary measures, such as attributable risk, can be estimated with this method.

Case-control studies have more to offer air pollution research than has been recognized. But uncertainties involved in retrospective exposure assessment still limit their use when precise information on dose-response relations or thresholds is needed.

INTERVENTION STUDIES

In intervention (experimental) studies, an investigator adds to or reduces exposures of a cohort and then follows the cohort, assessing the impact of the intervention on disease rates in comparison with rates in a control population. When a pool of suitable subjects is randomly divided between exposure and control groups, results are solidly based. In medical intervention, this approach (the randomized clinical trial) is widely recognized as the "gold standard" for strength of inference and proof of causality. Obviously, air pollution exposures cannot be deliberately imposed on a population, nor is the study of populations placed by chance at potential risk without ethical complications. The study of populations with reduced exposures is the most acceptable alternative. This strategy was used by investigators in England after the Clean Air Act in 1956 caused a great reduction in air pollution in most urban areas. The investigators tracked disease rates and compared them over time with the changing degree of air pollution and found that areas with greater reductions in smoke pollution experienced greater declines in lung cancer death rates.[14]

SPECIAL OPPORTUNITIES FOR AIR POLLUTION STUDIES

Occasional situations provide opportunities to expand and deepen the inferential base on a particular research question, by virtue of their peculiarities. These opportunities, which are somewhat indirect approaches to the question, can also be unusually cost-effective. The direct, deliberate design and organization of traditional epidemiologic studies are only part of what is required for an effective air pollution research strategy. The other part is the recognition and use of these special, and perhaps fleeting, situations for study.

Several types of special opportunities for research in air pollution are discussed in the following pages. Some pertain to rapid response or surveillance, some are settings for the development of protocols, and some are ways of asking new questions by building on current and continuing surveys or studies. Many of these are valuable because they allow epidemiologists to deal with major methodologic constraints. To some extent, the pursuit of information about the association of air pollution and illness in the United States is limited by the number of situations in which observational epidemiology can be conducted. Five important types of situations can be identified: extrapolation from unusually high or low exposures, dramatic increases or decreases in air pollution, the discovery of populations that avoid confounding variables, separation of ordinarily correlated exposures, and exposure of populations to pollutants of concern for the future.

OUTBREAK DETECTION AND RESPONSE

Daily or weekly changes in air pollution constitute opportunities to learn more about acute effects. Although the most sensitive studies rely on the proper placement of specially designed air monitoring and health evaluation systems, much can be learned by surveillance over wide areas with relatively crude exposure and effect data. Once an outbreak of pollution-related disease has been detected, more detailed studies can be set in motion. However, as mentioned in Chapter 2, better descriptive data on respiratory morbidity will be needed. Coupled with data from the national air monitoring systems, these data could form a surveillance network capable of detecting much smaller events than the fog disasters of previous decades.

Relatively crude outcome data are being collected in several systems. The Centers for Disease Control collects and compiles year-round information on total excess mortality and pneumonia and influenza deaths for 132 cities. Information on daily mortality, hospital censuses, and school and work absences is readily available in many areas. Although the limitations of these data are obvious, time-series analyses of specific populations can provide useful exploratory information.

OCCUPATIONAL STUDIES

Occupational cohorts are relatively easy to assemble for studies, and exposure measurement, at times based on personal monitoring, is often available. Although it is hard to find occupational groups exposed only to the major air pollutants, each one found is likely to have major value. For carbon monoxide, radon, and lead, occupational studies have formed a large part of the risk assessment model for community-wide exposure. Use of occupational studies for air pollution research is further complicated by the greater intensity and different temporal patterns of the exposure involved and by the "healthy-worker" characteristics of the population at risk. But cohorts appropriate for studies can be identified. Examples include flight crews and attendants exposed to ozone, corn refinery plant workers exposed to sulfur dioxide,[8] and professional cooks exposed to gas-stove emission, including nitrogen dioxide.

These occupational panels provide few opportunities to detect thresholds, but experiences can be particularly useful in constructing other parts of the dose-response curve and in validating new techniques for exposure or effect assessment, including biologic markers.

Kilburn and co-workers, after a study designed to examine the effects of para-occupational exposure to asbestos on wives and daughters of shipyard workers, reported the serendipitous finding of an effect on pulmonary function that might have been due to ambient air pollution.[11]

MIGRANT STUDIES

Studies of migrants have been useful in disentangling the effects of environment and heredity on disease incidence. In the field of air pollution, epidemiologists have used such studies to establish what is known as a "British effect," referring to residual excess risk of lung cancer and chronic bronchitis in British-born migrants, compared with native populations in the countries to which they migrated.[22] Thus, hereditary factors aside, migrants are interesting subjects for study because of the sharp changes in exposure that they might have experienced after emigration. Clues as to the impact of early exposure on the ultimate risk of chronic disease might also be revealed in these groups.

Residential mobility within the United States, which complicates local studies, can be turned to advantage by identifying groups that have moved between areas with sharply constrasting pollution conditions. Examples include the migration of rural people to cities, such as Los Angeles, and the movement of city residents to retirement communities in the Southwest. By examining the health changes that accompany these moves, we can in effect ask a series of "what if" questions regarding the potential impact of changes in air quality. Questions concerning the influence of past exposure on current response (adaptation, in toxicologic terms) might also be addressed with this approach.

PRISTINE POPULATIONS

We accept some air pollution as an inevitable accompaniment of contemporary industrial society, but we have only scant knowledge about the general health status that we might observe if we had little or none at all. In particular, the shapes of growth and decay curves for lung function in the absence of substantial air pollution are not known. Research in Busselton, Australia, is attempting to describe lung growth and decay curves measured longitudinally in a large, nonexposed population of European descent (personal communication, A.C. Woolcock, University of Sidney, New South Wales, Australia). Until this kind of information is available, it will be hard to rule out a subtle but pervasive effect of air pollution on respiratory function. The range of function considered normal might in fact be abnormal compared with that in pristine populations. For example, normal serum cholesterol differs between the United States and Japan, and normal blood lead content differs between a Himalayan population and the general U.S. population.[19] As Rose has recently stated, the most difficult risk factor to detect epidemiologically is one that is present in every member of the population.[23]

POINT-SOURCE POLLUTION

In communities near single point sources of pollution, collection of precise data on emission and exposure modeling of the population are often feasible. Moreover, the population at risk is often well-defined and might be contained within administrative units conducive to the organization of an epidemiologic study. Of primary interest, however, is the possibility that communities near point sources have exposure that is relatively uncomplicated by the presence of multiple pollutants. Such conditions can be found in small towns with little industry or automobile traffic. Towns near paper mills (sulfur dioxide), chemical plants (various volatile hydrocarbons), and smelters (particles, sulfur oxides, and heavy metals) are some examples. The selection of a small community for study could constrain sample size and, hence, statistical power; such problems should be considered during study planning.

STUDIES OF POPULATIONS IN FOREIGN COUNTRIES

Some overseas populations have had long-term exposure to air pollution at magnitudes no longer seen in the United States. Many of these populations are in semi-industrialized cities with crowding and substantial automobile traffic. Because of the exaggerated contrasts in pollution, these cities might provide ideal sites for studies involving questions of the "any association" type. Downward extrapolation along dose-response curves could also prove feasible. Figure 6 shows results in selected cities from a global monitoring survey of annual average sulfur dioxide concentrations.

Some cities in other countries have experienced rapid industrialization and urbanization with concurrent swift

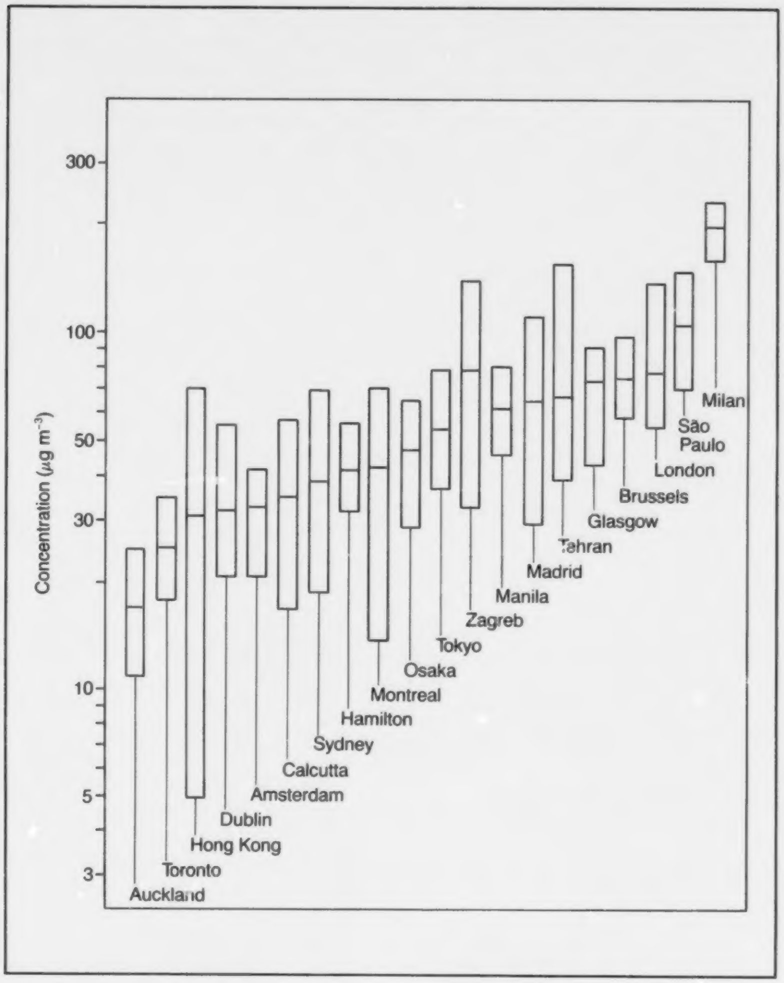


FIGURE 6 SO_2 in cities of the GEMS monitoring network, 1976-1980. Range of annual averages at individual sites and composite average for each city. Reprinted with permission from Bennett.[1]

increases in pollution. In Sarajevo, Yugoslavia, for example, atmospheric emission of nitrogen oxides increased by 277% between 1970 and 1980.[3] Health in areas with a longer history of modernization might have deteriorated so gradually as to defy detection. Dramatic decreases in exposure to a pollutant or mixture can also occur in cities undergoing rapid conversion from one fuel source to another.

Elimination of a confounding variable, such as smoking or occcupation, through selection of a study population is sometimes more effective than using matching, stratification, or multivariate adjustment techniques in the study design or analysis. For example, one could minimize the impact of indoor versus outdoor exposure by studying groups that live in tropical or subtropical climates, where building techniques allow ample ventilation and people spend greater proportions of their time outside. Situations outside the United States should be sought in which it is possible to separate the effects of exposures that are normally coexistent. For example, sulfate concentration might be high in the presence of low concentrations of particles or ozone, or nitrogen oxide concentration might be high in the presence of low concentrations of other photochemical oxidants.

It is important to maximize the benefit derived from expensive longitudinal studies and to disseminate their methods and results as widely as possible. The investment of U.S. effort and funds in studies already going on in other countries could be more prudent, in some instances, than starting similar studies here. For example, U.S. expertise in monitoring and health effects technology can be used to complement and strengthen some studies. Longitudinal studies of note are being conducted in Canada (Hamilton),[18] the Netherlands,[25] and Brazil (personal communication, H. P. Ribiero, Department of Surgery, School of Medical Sciences of Santa Casa, Sao Paulo, Brazil).

The existence of centralized and universal health insurance coverage in other countries (for example, Canada and Sweden) might provide data on which powerful and cost-effective studies could be based.

Many nations have responded to the 1973 world oil crisis by reviving the use of traditional fuels and exploring alternative technologies. Several fuels--such as coal, wood, and gasohol--are being considered as alternatives to oil in the United States, but there is little information on their potential adverse health effects. Learning from the evolving experience in other countries might prevent costly and unhealthful mistakes or inspire innovative technologies. For example, 90% of the cars manufactured in Brazil are designed to run on fuel that contains a large proportion of ethanol; this will result in a massive shift in the pattern of air pollution in some Brazilian cities, and it is already raising questions about the potential health effects of combustion products, such as aldehydes (personal communication, R. Mendes, Pan American Health Organization).

ADAPTATION OF EXISTING COHORT STUDIES

The remaining special opportunities concern the design of highly powerful and cost-effective epidemiologic studies through adaptation or "piggy-backing" of air pollution hypotheses onto longitudinal studies or surveys. In some instances, cohorts established for other purposes may be adapted to address air pollution questions. The wealth of data from the Framingham and Tecumseh studies was mentioned earlier. Other longitudinal studies of respiratory health have been conducted in Tucson,[12] Baltimore,[4] and Boston.[26] Statistical models designed to predict the risk of COPD have been applied to each cohort.[10] These models confirm that age, sex, smoking habits, and initial FEV_1 are the most important factors in predicting development of COPD within 10 years of initial evaluation. Air pollution exposure has not yet been thoroughly tested in all the cohorts. It is unlikely that air pollution exposure will match the above variables in significance or substantially improve the predictive power of the models for general populations, but it is conceivable that some indexes of air pollution exposure would prove to be predictors of COPD in a particular cohort. The adaptation of existing data or the incorporation of new data on exposure in these cohorts should be explored.

Many data sets covering the health status of numerous people are assembled or updated each year by branches of the federal government, by state and local governments, and by private companies. Air pollution researchers should be aware of these epidemiologic opportunities, so that they can work with data assemblers to shape the collected data. Through piggybacking on existing data-collection efforts, useful hypothesis-generating studies might be performed, with substantial economies of scale.

Perhaps the best examples of such opportunities are several surveys conducted annually (or in some cases less frequently) by the National Center for Health Statistics (NCHS). For instance, each year since the early 1970s, NCHS has randomly surveyed (in the Health Interview Survey, HIS) about 120,000 people, constituting about 40,000 households in all parts of the United States, to determine the health status of the entire population. Data are available in the HIS on many of the variables for which one would want to control in an epidemiologic study. The health component of the HIS includes questions on acute illnesses during a 2-week period before the interview and on chronic illnesses. Although acute respiratory diseases have recently been studied in this manner, the utility of the HIS data for studies of the relation between air pollution and chronic disease remains to be explored.[21]

Another survey conducted by NCHS, the National Health and Nutrition Examination Survey (NHANES), is in some respects a potentially more valuable epidemiologic tool. Like the HIS, the NHANES elicits information on important socioeconomic and other characteristics of the respondents. However, in addition to respondent-provided data on acute and chronic illness, the NHANES contains data from physician examinations and medical tests involving each respondent. The latter include data on pulmonary function, blood lead content, carboxyhemoglobin content, concentrations of toxic substances in blood or urine samples, and other potentially valuable items. The data might be most profitably merged with air pollution exposure data for generating hypotheses.

Both the HIS and the NHANES could benefit from modifications to make them better epidemiologic instruments without detracting from their primary purpose. For instance, neither regularly provides as much information on lifetime smoking history as would be desirable (although excellent supplements are occasionally added to each). Similarly, it would be desirable to have more complete data on individual residential and occupational histories, exercise and other personal habits, and perhaps even preventive and curative medical expenditures.

In an effort to uncover other data sets of potentially high value but relatively low cost, research planners should investigate the possibility of working with insurance companies, providers of prepaid health care, and agencies that collect DRG records on hospital admissions. In some cases, such groups might have mortality and morbidity data of high quality coupled with data on residential histories. These latter data are important if links between air pollution and chronic illness are to be investigated. By the same token, some international data bases might have great utility in epidemiologic analyses. Data from countries that have national health-insurance programs might permit not only cross-sectional analysis, but also time-series or longitudinal studies. These data, if available, will be most useful if they originate in countries where ambient air pollution data are of high quality.

COST AND INFORMATION

The feasibility and limits of epidemiologic strategies are determined by their costs, as well as by their benefits. Estimating the productivity and cost-effectiveness of various ways to answer specific questions has become an integral part of epidemiologic research planning. For this purpose, benefits are usually conceived of as information value--the degree to which the study's results bridge the gap between the question and its definitive answer or provide spinoff knowledge for other studies. The benefits of a particular study are a function of its pertinence and of the quality and amount of information it delivers. Comparisons of the relative productivity of optional research strategies and studies might contribute more than any other planning effort to the establishment of research priorities and the ultimate refinement of question and design.

Cost considerations can enter at two levels of planning. At the individual study level, the investigator strives to reduce costs as much as possible without compromising the information value of the study. At the strategic level, the planner balances information needs versus costs and distributes many kinds of resources over a collection of studies. Planning at these two levels is interdependent, because the relative costs of possible studies are needed as input in the development of the research strategy, and the evolution of the strategy determines which study designs receive the most thorough cost estimation. Cost and productivity analysis must be viewed as an inherent part of the process of planning overall strategy, and not simply in terms of proposals for individual, isolated studies.

The range of epidemiologic study costs is particularly wide, and the relationship between cost and information value is remarkably unpredictable. Some very inexpensive studies provide information of enormous value, and some large and expensive ones contribute little. The inferential value of a study often has more to do with its timing and context than with its cost. In most air pollution studies, it is easy to spend large amounts of money by directing resources at the wrong potential sources of error. For example, greater precision in exposure measurements might be unprofitable if sample sizes are inadequate or study populations are poorly characterized.

A research program that aims to produce the best possible epidemiologic studies will have to include funding for complementary nonepidemiologic research, including methodologic and technical development and exposure characterization. Technologic research and development, designed to provide better tools for exposure and effect assessment, must be closely woven into epidemiologic research strategies. Some of the barriers to progress are technologic, just as others stem from ignorance of the biology of disease or the limitations of study method. From the viewpoint of the strategic research planner, investment in critical technology is cost-saving--when appropriate technology is lacking, it might be impossible to answer contemporary questions within reasonable costs. The removal of technologic constraints can often be hastened if scientists clearly specify their needs for research and development. An obvious example is the lack of a personal monitoring badge for nitrogen dioxide that can measure short-term exposures. The limits of epidemiologic research depend in part on the changing state of the art of measurement in several disciplines, so they differ from one problem to another and from one time to another.

THE MILIEU OF EPIDEMIOLOGIC RESEARCH

The development of productive epidemiologic strategies in a difficult field like air pollution research will require time, organization, and patience. The creation of the necessary milieu for such research depends on several factors:

- Stable administrative and financial support.
- Adequate amounts of overall funding.
- An appropriate range of contact with sponsoring and regulatory agency personnel.
- Provisions for training and career development of new scientists.
- Opportunities for assembling multidisciplinary research groups consisting of epidemiologists, atmospheric scientists, statisticians, and health effects scientists.
- Opportunities for interaction among epidemiologists, clinicians, and toxicologists.

Some potential adverse health effects of current air pollution can be detected only through serial observations over time. Such studies often entail followup of population groups for several years by well-organized research teams led with an exceptional degree of administrative skill. Successful examples of long-term studies include the 25-year British study of a cohort of children from birth to young adulthood and the Harvard Air Pollution Health Study of the growth and decay of lung function.[5,26] The need for administrative and financial stability also applies to a sequence of closely linked studies. The Environmental Protection Agency's record of support for epidemiologic studies since 1970 is one of cataclysmic variation, from strong support to nearly complete withdrawal of funds, in spite of heavy reliance on epidemiologic research for risk assessment and standard-setting. A minimal long-term base budget for epidemiologic studies should be considered. With it, the research community could develop confidence in the stability of resources necessary for long-term studies of exposed populations.

The conduct of long-term studies or of a sequence of studies in a research strategy relies on some degree of isolation from short-term changes in federal research managers and agency priorities. However, a portion of the epidemiologic research program should have the flexibility to respond quickly to short-lived opportunities or demands and in so doing work closely with research sponsors and regulators.

The expertise for designing and conducting epidemiologic studies of air pollution is a rare resource that, once established, needs to be cultivated and maintained. Mechanisms to encourage the training of qualified epidemiologists and to assist in their career development are needed. Continued failure to provide the appropriate milieu for studies will have a downward-spiraling effect: many young and qualified investigators will avoid air pollution problems--a situation that will lead to a further decline in the performance of epidemiologic studies, which in turn impedes the recruitment of new trainees.

The successful completion of epidemiologic studies on air pollution requires a continuing collaboration among members of various disciplines, including epidemiologists, atmospheric scientists, health effects scientists, and statisticians. It is essential that all members of a research team be active in the initial planning of a study to optimize the use of pertinent information and tools available from different fields. Monitoring specialists must be involved in population selection on the basis of characterization data and must help determine which types of exposure data need to be collected to evaluate the biologic model of concern. It is equally important for health effects scientists to be involved in planning, to ensure that the biologic markers or indexes of specified health effects are matched to the pollutants being monitored. The sensitivity and specificity of techniques, the appropriate time for sampling, and the doses of material received by target organs need to be considered. Statisticians are essential in planning, to help to ensure that data of the appropriate type and amount will be collected and that problems in data reduction, modeling, and analysis are anticipated.

The difficulty and necessity of establishing multidisciplinary groups in the framework of existing academic and government research institutions must be recognized. And it is necessary for the epidemiology units to interact with clinicians and animal toxicologists in the same or other institutions. Five-year grants, specialized centers of research, and multiyear cooperative agreements are some of the mechanisms possible for creating stable and productive research groups. It is important to incorporate appropriate peer review of these centers and long-term projects into the funding process, to help to ensure quality.

EPIDEMIOLOGIC DATA AND THE REGULATORY PROCESS

At the heart of the regulatory process for ambient air pollutants in the United States is the determination of approximate "safe" exposures to specific pollutants. In some instances, for some aspects of the standards, epidemiologic data can provide the direct basis for such determination. In other instances, epidemiologic studies cannot yet provide the type of quantitative answer required for control of a particular pollutant. Even in the latter case, the determination of a standard will hardly rely on a single definitive study, and standard-setting inevitably involves the careful weighing of many pieces of evidence of various kinds. It is often not recognized that it is the cumulative force of different studies (each of which could be faulted in one respect or other) that gives strength to the data. Each piece of evidence can contribute to regulatory decisions; in the process of making regulatory decisions, the nature and extent of the uncertainty attached to each piece must be carefully evaluated.

Although the proper domains of "science" and "regulation," or risk assessment and risk management, are becoming well understood, problems of communication remain. Those charged with the responsibility of making decisions might find it difficult to understand why straightforward answers to simple questions are not forthcoming. Attempts (praiseworthy in themselves) to avoid overinterpretation of data can be interpreted as disbelief in the significance of any data; efforts to reduce what must remain subjective to a formal quasi-mathematical process, which the data base might be too fragile to support, might mislead those who are unfamiliar with the details of studies into believing that the data are stronger than they really are.

Such difficulties cannot be resolved by refinement of data, although that is always desirable. What is needed is the opportunity for those who analyze the data in detail or participate in collecting them to exchange ideas with those who are involved with policy, until each side is sure that the other fully grasps the strengths and weaknesses of the data being relied on. One of the objectives of this chapter has been to describe how uncertainty in epidemiologic studies of air pollution might be characterized, so that it can be captured and conveyed properly to policy-makers. This uncertainty must be weighed against the uncertainty that has been built into the process for setting standards and margins of safety.

Epidemiology has many uses in protecting the public from air pollution, beyond the setting of specific standards. Epidemiologic studies can point out areas or major pollution sources that need regulation or some form of intervention and can monitor the health of communities, to assess the results of favorable or unfavorable changes in pollution. Research that is directly applicable to standard-setting should not always take priority over research that is needed for the understanding of broader health issues.

Finally, evidence of safety is not the converse of evidence of risk; safety is often much harder to demonstrate. That is the critical difference between the interpretation of studies that find an effect and studies that do not. There are several reasons for the difference: statistical power of studies might be adequate to show large effects, if they are present, but not to exclude smaller effects that are of regulatory interest; nonrandom errors might be more easily dealt with in positive studies; clear demonstration of an effect in one population segment might create a presumption of effects elsewhere that is not balanced by similarly clear demonstration of the lack of effects in other segments; and control measures might be required if a small part of the population is affected, but not rendered superfluous if a large part is shown to be unaffected. Thus, good large studies with negative results can often have less meaning than smaller poorer studies that are positive. Fairness is not the issue; negative studies, no matter how large and well conducted, can rarely be used to exclude important health effects in other populations and other circumstances.

REFERENCES

1. Bennet, B.G., J.G. Kretzschmar, G.G. Akkland, and H.W. de Koning. Urban air pollution worldwide. Environ. Sci. Technol. 19:298-304, 1985.

2. Berry, G. Longitudinal observations: Their usefulness and limitations with special reference to the forced expiratory volume. Bull. Physio-pathol. Respir. 10:643-655, 1974.

3. Cerkez, R., and A. Knezevic. Study of Pollution and Management of the Environment in the Urban Area of Sarajevo. Sarajevo, Yugoslavia: Institute of Hygiene and Environmental Protection and Radiological Protection, 1983. 60 pp.

4. Cohen, B.H., W.C. Ball, Jr., W.B. Bias, S. Brashears, G.A. Chase, E.L. Diamond, S.H. Hsu, P. Kreiss, D.A. Levy, H.A. Menkes, S. Permutt, and M.S. Tockman. A genetic-epidemiologic study of chronic obstructive pulmonary disease: 1. Study design and preliminary observations. Johns Hopkins Med. J. 137:95-104, 1975.

5. Colley, J.R.T., and D.D. Reid. Urban and social origins of childhood bronchitis in England and Wales. Br. Med. J. 2:213, 1970.

6. Ferris, B.G., Jr., F.E. Speizer, J. Worcester, and H.Y. Chen. Adult mortality in Berlin, N.H., from 1961 to 1967. Arch. Environ. Health 23:434-439, 1971.

7. Glindmeyer, H.W., J.E. Diem, R.M. Jones, and H. Weill. Non-comparability of longitudinally and cross-sectionally determined annual change in spirometry. Am. Rev. Respir. Dis. 125:544-548, 1982.

8. Greaves, I., B.G. Ferris, Jr., W.A. Burgess, and D. Essex. Respiratory effects of sulfur dioxide (SO_2) among corn refinery workers. Am. Rev. Respir. Dis. 129:157, 1984.

9. Higgins, I.T.T. Trends in respiratory cancer mortality: In the United States and in England and Wales. Arch. Environ. Health 28:121-129, 1974.

10. Higgins, M.W., J.B. Keller, J.R. Landis, T.H. Beaty, B. Burrows, D. Demets, J.E. Diem, I.T. Higgins, E. Lakatos, M.D. Lebowitz, H. Menkes, F.E. Speizer, I.B. Tager, and H. Weill. Risk of chronic obstructive pulmonary disease: Collaborative assessment of the validity of the Tecumseh index of risk. Am. Rev. Respir. Dis. 130:380-385, 1984.

11. Kilburn, K.H., R. Warshaw, and J.C. Thornton. Pulmonary functional impairment and symptoms in women in the Los Angeles Harbor Area. Am. J. Med., 1985. (in press)

12. Lebowitz, M.D., R.J. Knudson, and B. Burrows. Tucson epidemiologic study of obstructive lung diseases: I. Methodology and prevalence of disease. Am. J. Epidemiol. 102:137-152, 1975.

13. Mason, T.J., J.F. Fraumeni, Jr., R. Hoover, and W.J. Blot. An Atlas of Mortality from Selected Diseases. NIH Publication No. 81-2397. Bethesda, Md.: U.S. Department of Health and Human Services, National Cancer Institute, 1981. 309 pp.

14. Monson, R.R. Occupational Epidemiology. Boca Raton, Fla.: CRC Press, 1980. 219 pp.

15. Morgenstern, H. Uses of ecologic analysis in epidemiologic research. Am. J. Pub. Health 72:1336-1344, 1983.

16. Morris, J. Uses of Epidemiology. New York: Churchill Livingstone, 1975. 262 pp.

17. Pan American Health Organization. Red Panamericana de Muestro de la Contaminacion del Aire, Informe Final 1967-1980. (Pan American Network for the Sampling of Contaminated Air, Final Report 1967-1980). Serie Technica No. 23, 1982. 65 pp.

18. Pengelly, L.D., A.T. Kerigan, C.H. Goldsmith, and E.M. Inman. The Hamilton study: Distribution of factors confounding the relationship between air quality and respiratory health. J. Air Pollut. Control Assoc. 34:1039-1043, 1984.

19. Piomelli, S., L. Corash, M.B. Corash, C. Seaman, P. Mushak, B. Glover, and R. Padgett. Blood lead concentrations in a remote Himalayan population. Science 210:1135-1137, 1980.

20. Polissar, L. The effect of migration on comparison of disease rates in geographic studies in the United States. Am. J. Epidemiol. 111:175-182, 1980.

21. Portney, P.R., and J. Mullahy. Urban air quality and acute respiratory illness. J. Urban Econ. (in press)

22. Reid, D.D., J. Cornfield, R.E. Markush, S. Siegel, E. Penderson, and W. Heintzel. Studies of disease among migrants and native populations in Great Britain, Norway, and the United States: III. Prevalence of cardiorespiratory symptoms among migrants and native-born in the United States. Nat. Cancer Inst. Monogr. 19:321-346, 1966.

23. Rose, G. Sick individuals and sick populations. Int. J. Epidemiol. 14:32-38, 1985.

24. Tashkin, D.P., V.A. Clark, A.H. Coulson, M. Simmons, L.B. Bourque, C. Reems, R. Detels, J.W. Sayre, and S.N. Rokaw. The UCLA population studies of chronic obstructive respiratory disease: VIII. Effects of smoking cessation on lung function: A prospective study of a free-living population. Am. Rev. Respir. Dis. 130:707-715, 1984.

25. Van der Lende, R., T. Kok, R. Peset, Ph.H. Quanjer, J.P. Schouten, and N.G.M. Orie. Longterm Exposure to air pollution and decline in VC and FEV_1: Recent results from a longitudinal epidemiologic study in the Netherlands. Chest 80(Suppl.):23S-26S, 1981.

26. Ware, J.H., Thibodeau, L.A., F.E. Speizer, S. Colome, and B.G. Ferris, Jr. Assessment of health effects of atmospheric sulfur oxides and particulate matter: Evidence from observational studies. Environ. Health Perspect. 41:255-276, 1981.

27. Willett, W.C., B.F. Polk, B.A. Underwood, and C.G. Hames. Hypertension detection and follow-up program study of serum retinol, retinol-binding protein, total carotenoids, and cancer risk: A summary. J. Nat. Cancer Inst. 73:1459-1462, 1984.

Chapter 5

The Application of Epidemiology to Selected Research Questions

5

THE APPLICATION OF EPIDEMIOLOGY TO SELECTED RESEARCH QUESTIONS

INTRODUCTION

This chapter uses several case studies to illustrate how epidemiologic strategies and study designs involving both long-term planning and flexible short-term responses can be applied to important current research questions. We have stressed that the development of protocols for epidemiologic research in air pollution requires substantial amounts of focused interdisciplinary planning and coordination. Therefore, the purpose of this chapter is not to write protocols for specific studies. Instead, for each selected problem dealt with here, we recommend approaches or guides to particular components of strategy and design development. The following components are addressed:

- Selection of a study method.
- Selection of study populations.
- Selection of exposure variables.
- Selection of effect variables.
- Selection of confounders to be considered.
- Special opportunities for studies to be considered.
- Limitations on the types of answers possible.

ACUTE RESPIRATORY INFECTION

"Do any current patterns of exposure to air pollutants lead to increased frequency or severity of acute respiratory infections?"

The study methods likely to be of use for this particular question are the prospective cohort method and the case-control method. Ecologic studies are not foreseeable, because widely reported data on the incidence of these conditions are lacking. The prospective cohort method requires the study of a relatively common end point, perhaps upper respiratory infections, as opposed to more serious lower respiratory infections (such as acute bronchitis and pneumonia). To achieve acceptable statistical power with the cohort method in studying less common events, large numbers of people must be followed for long periods, and that creates problems related to expense and the potential for loss of subjects to followup.

However, small cohorts (panels) of children could provide a sensitive basis for studies. The high frequency of acute respiratory infection among preschool children (four to eight episodes per year) makes it possible to detect even small increases in the relative risk among exposed populations. Thus, an increment of 25% typically could be detected readily in a population of 200-300 children, whereas such small increments in chronic disease prevalence would require several thousand person-years of observation. Acute respiratory infection in children is readily detected and reported by most parents, but frequent contact with subjects or their parents is necessary, because the events are short-lived and easily forgotten. Methods to validate the presence of an acute respiratory infection might present themselves when our ability to measure immune responses in humans has advanced.

Case-control methods might work nicely for the study of serious but infrequent infections. Acute bronchiolitis in infants, for example, can be caused by a number of viruses and is a frequent reason for hospital admission of children under the age of 2. Such infections have been linked with a later risk of developing chronic obstructive pulmonary disease (COPD).[21] Cases of bronchiolitis can readily be accumulated by active pediatric hospital services, and the diagnoses can be accurately verified, with viral antibody titers or cultures if necessary. Controls could be selected from infants admitted with diagnoses not conceivably related to air pollution. The youth of the subjects and the acute nature of the illness make it fairly easy to determine lifetime exposures, both inside and outside the home. Exposures are recent enough to permit monitoring in homes for specific pollutants or for particular emission sources, perhaps for a sample of the study group.

The specific pollutants of interest in studies of respiratory infection might be nitrogen oxides, gas stove emission, passively received cigarette smoke, woodsmoke, acid aerosols, and recurrent summertime haze and ozone. If a small-cohort frequent-event approach is taken, it should be possible to use individual, rather than aggregate, monitoring data on pollutant exposure. With a large cohort, individual measurements could be made on a sample to "anchor" or validate the aggregate data.

Cigarette smoking would be a serious confounding variable in any studies in this field, and it is tempting to restrict studies to children or nonsmokers. But the exclusion of smokers from all studies would be a serious mistake, because cigarette smoke and air pollution might act synergistically to multiply the risk of developing a respiratory infection. Smokers would therefore constitute a useful hypersusceptible or sensitive population for study. Furthermore, nonsmokers might be subjected to some degree of risk through passive exposure. Besides the usual confounders, studies of acute respiratory infection will have to deal with unusual and difficult codeterminants of risk, including epidemics in the community, social class, season, number and age of siblings, and frequency of contact with other people.

Some special opportunities for studies in this field can be identified. The utility of national survey samples--such as the National Health Information Survey--will be increased by improvements in routinely collected pollution surveillance data. Countries or regions with centralized health services can provide excellent opportunities for studies that require the recording of discrete events, such as hospital admissions due to respiratory infection.[4] Finally, epidemiologic surveillance systems that track the response of respiratory infection rates in communities to fluctuations in pollution could prove useful as a preliminary form of study.

The use of small cohorts with individual exposure measurements could be a particularly sensitive means for studying the impact of small excursions above existing air quality standards. This is one of the circumstances in which epidemiologic studies might be able to give answers to threshold questions. The other study designs mentioned above are better suited to "any-association" or "dose-response" questions, depending largely on the extent of detail in the exposure data. Obviously, studies based on categorical data (e.g., frequency of use of gas stoves, woodstoves, or kerosene heaters) will be less suitable for the construction of dose-response curves than studies based on continuous numerical data. Many studies of acute respiratory infection will be able to determine which among numerous pollution sources is responsible for an effect. But few of them, even if conducted with individual measures of several pollutants, will easily be able to attribute an effect to a specific pollutant.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

"Do any current patterns of exposure to air pollutants lead to an excess risk of developing chronic obstructive pulmonary disease (COPD) or to exacerbation of existing COPD?"

In many ways, this is the most difficult question for epidemiologic studies and therefore the one that requires the greatest care and ingenuity. The incidence of COPD is relatively low, so prospective studies that use clinical cases to determine the etiologic role of air pollution are unfeasible, for reasons of cost and time. That leaves two alternative strategies: studying the onset of COPD retrospectively and studying the development of early markers (physiologic or biochemical) that presage the clinical disease.

All retrospective methods for studying this question suffer from the lack of reliable, precise data on individual lifetime exposure to ambient pollutants. A case-control study of COPD would be attractive if this difficulty could be overcome. Given lifetime residential histories obtained through interview of the subjects, some index of cumulative exposure to pollutants could be constructed. It would probably require expert subjective assessment of pollution in various locales at various past times, inasmuch as measurements would not likely be available for the early years of the subjects' lives. This approach is not unlike the one common to retrospective studies of occupational cohorts, except that fewer variables need to be considered in reconstructing workplace exposures. The result would be a cumulative pollution exposure index that would be relatively coarse and insensitive to the role of individual pollutants.

A case-control study of nonsmokers with COPD is worth considering because of the major etiologic role of smoking in most cases. The incidence of COPD in nonsmokers, however, is extremely low and would necessitate collaboration of several medical institutions for assembly of an adequate number of cases. (For example, in the Tucson cohort, the prevalence of COPD in nonsmoking adults was 2 per 1,000 persons.[13]) If air pollution causes COPD, it probably causes more cases among smokers than among nonsmokers; therefore, studies that yield information about the interaction of smoking and air pollution in the etiology of COPD would be extremely valuable.

That brings us back to the prospective cohort method. It is the most effective means for addressing the question of COPD etiology, if costs can be kept down and the precision of exposure information and sample size can be maintained. It should soon be possible to develop predictive biochemical tests that capitalize on early injury to connective tissue in COPD. So far, the studies directed at detecting degradation products of elastin and collagen appear promising. The use of rapid decline of FEV_1 or of other measures of pulmonary function as markers of COPD is desirable, in that rapid decline is far more common than clinically apparent disease; etiologic studies can therefore be shorter and cheaper and have satisfactory statistical power.

Berry, Schlesselman, and others have shown that varying the number of subjects followed, the frequency of lung function measurement, and the length of followup makes it possible to maximize the chances of detecting an effect of a given magnitude without wasting resources on excess measurements.[6] [22] Table 1 shows the numbers of

TABLE 1

LONGITUDINAL OBSERVATIONS

Number of Subjects Required in Followup Study of FEV_1
in Each of Two Groups, to Detect Differences of 0.03 L/year
at Significance Level of 0.05 and Power of 0.8[a]

Length of Followup, years	Intervals Between Measurements					Cross-Sectional Study on Subjects Previously Exposed for Length of Followup
	1 Month	3 Months	6 Months	1 Year	Beginning and End Only	
1	226	429	530	530	530	4,356
2	56	95	128	153	153	1,089
3	36	50	64	78	84	484
4	32	38	45	53	59	272
5	30	33	37	42	48	174
6	29	31	33	37	42	121
7	29	30	31	34	38	89
8	28	29	30	32	36	68
9	28	29	30	31	34	54
10	28	29	29	30	33	44

---

[a] Reprinted with permission from Berry.

subjects required for different followup periods. In fact, only small panels of subjects (fewer than 100 in the "exposed" cohort) are required, if followup extends for 3 years and measurements are taken only once a year. Therefore, a large study can follow several cohorts simultaneously, each with a different pattern of pollution exposure. The inclusion of multiple cohorts mitigates the "sample size of two" problem encountered in some large cohort studies that use only two kinds of populations (see Appendix C). Perhaps more important, the use of small cohorts makes it easy to incorporate precise individual exposure measurements or to apply them to a substantial fraction of each cohort.

Cross-sectional studies on the COPD question should not be ignored. The first slice in time looked at in a longitudinal study might be suitable for analysis as an independent cross-sectional study. This requires planning from the beginning, to ensure that estimators of past exposure are available at baseline. Furthermore, the last column in Table 1 shows that appreciable power can be achieved in a cross-sectional study, if the population consists solely of subjects who have had several years of exposure before testing. For example, in a two-population study ("exposed" and "nonexposed"), only 174 persons exposed for a period of 5 years would have to be studied to meet standard power requirements. As previous discussions have pointed out, however, this consideration accounts only for random errors; in the case of cross-sectional studies of chronic respiratory disease, the nonrandom error associated with retrospective exposure assessment would be a dominant concern and would limit the types of answers that could be expected.

A research strategy on the COPD question would be enhanced by prior consideration of descriptive data on COPD incidence or mortality. Such data (although not perfectly reliable) could be used to locate "hot spots," where the occurrence of pollution-related cases might be greatest. Figure 7 is a map of the United States showing the distribution of mortality from chronic bronchitis among white females between 1965 and 1971.[25] Mortality among women during this period would presumably be less influenced by smoking and occupational exposure than mortality among men. One potentially interesting area for the location of a study would be the Ohio Valley,

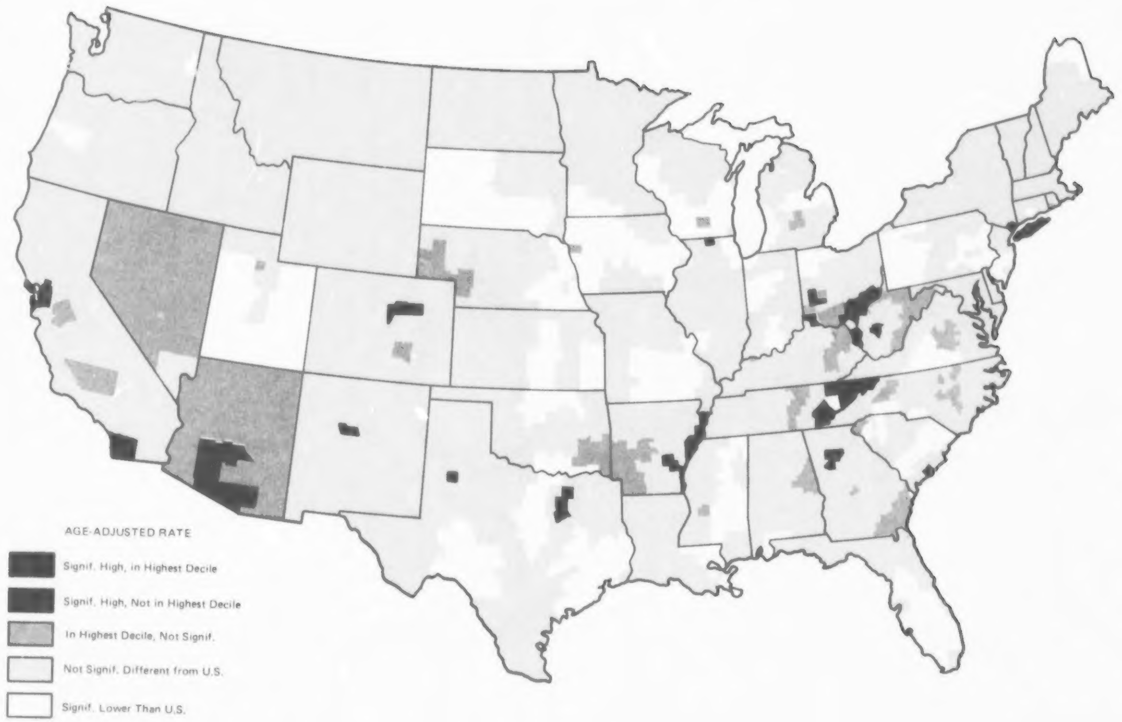

AGE-ADJUSTED RATE
Signif. High, in Highest Decile
Signif. High, Not in Highest Decile
In Highest Decile, Not Signif.
Not Signif. Different from U.S.
Signif. Lower Than U.S.

FIGURE 7 Chronic bronchitis mortality among white females, 1965-1971. Reprinted from U.S. Department of Health and Human Services.[25]

where mortality rates were particularly high in a multistate area that included worrisome pollution sources. Given the limitations of mortality data for respiratory disease across geographic boundaries, a preliminary ecologic study would not be advisable. However, pilot studies in an area of high rates can explore the role of local artifacts in diagnosis or reporting or the impact of confounders, such as smoking. Case-control studies should follow, and then perhaps cohort studies.

Special opportunities for studying the role of air pollution in the etiology of COPD might be found. One important opportunity could be provided by the anticipated decreases in the emission of acid-precipitation precursors in some areas. The impact of sudden decreases on the respiratory health of a surrounding population--for instance, in a community near a midwestern power generating plant--would be a potentially fruitful subject for a cohort study. The growth of lung function in children offers another opportunity. Rates of increase in such indexes as FEV_1 are sensitive indicators of toxic lung injury, according to recent studies on the effects of passive smoking and gas cooking.[27] Children who fail to reach their highest potential plateau have less reserve lung function and are presumed to be at greater risk of dangerous decline in function. The opportunity afforded by studies of heavily exposed occupational groups or populations abroad should not be overlooked.

Studies of the exacerbation of COPD call for a strategy entirely different from the strategy for COPD etiology, because exacerbation is considered acute, rather than chronic. Small cohorts (panels) of carefully screened subjects with chronic respiratory diseases can be followed longitudinally. In an approach very similar to that recommended for asthma or acute respiratory infection, the goal is to ascertain the determinants of the probability of exacerbation in a person over a given period. Personal monitoring can be incorporated into the design, to increase the precision of the study.

The kinds of answers that epidemiologic studies might provide on the COPD question depend largely on the accuracy of the exposure information used. Further development of biologic markers that indicate the breakdown of connective tissue in the lung will increase study sensitivity. Threshold questions on the etiology of COPD do not appear to be feasible within reasonable cost bounds, particularly for thresholds related to individual pollutants. In the future, the availability of better nationwide monitoring data on pollutants (collected since the 1960s) will provide a basis for accurate estimation of long-term cumulative individual exposure. Such data, when combined with data on individual effects, will permit a great increase in the overall power of almost any study method, except perhaps when outdoor exposure is a poor predictor of total exposure.

ASTHMA

"Do any current patterns of exposure to air pollutants lead to an increased risk of developing asthma or to exacerbation of existing asthma?"

It is unlikely that air pollution plays a major role in the etiology of asthma, although some brief but intense exposures like the Yokkaichi episode (involving sulfuric acid mist) in Japan apparently can increase the prevalence of the disease in a community.[12] Genetic factors, such as atopic status, are known to be important, so a good strategy might include twin studies to determine the relative contributions of genetic and environmental variables. Other studies related to asthma etiology will be constrained by the same kinds of factors as studies of COPD etiology. The relative rarity of new asthma cases makes case-control studies worthy of consideration, if problems with retrospective exposure assessment can be addressed.

Most epidemiologic studies of air pollution and asthma have focused on acute exacerbation of the disease--definitely a subject in which recent developments can be applied to increase the sensitivity of studies. In the future, small-cohort studies of asthmatics will be able to take advantage of advances in statistical techniques (time series or individual regression), personal monitoring for estimation of short-term exposures, and portable devices, such as the peak flow meter, for frequent recording of pulmonary function by subjects themselves. Such individual monitoring will automatically include exposures to indoor pollutants and allergens whose composition and concentrations have been shown to differ greatly from those prevailing outdoors. The preferred research strategy will follow several panels of asthma patients and controls over time. The panels might be of different socioeconomic, racial, or ethnic composition and might be subjected to different environmental conditions. As the number of subjects in a study increases, persons with similar dose-response patterns could be grouped, in recognition of the heterogeneity of the population labeled asthmatic.

Some epidemiologic studies of air pollution and asthma will be complicated by recent observations that asthma morbidity, reflected in hospital admissions, appears to be increasing in the United States and other parts of the world.[4] [16] [26] Air pollution is probably not responsible for these increases, which have occurred in spite of some notable therapeutic advances in the last 15 years. Nevertheless, until the reasons become clear, trend data on asthma morbidity in large populations and data covering long periods must be interpreted cautiously.

There is every reason to believe that the types of studies described in this report will soon be able to answer questions about the relationship between the frequency of asthmatic attacks and relatively minor fluctuations in exposure to specific pollutants.

LUNG CANCER

"Do any current patterns of exposure to air pollutants lead to an excess risk of developing lung cancer, and does this exposure interact with cigarette smoking in producing excess risk?"

Exploring the relationship between lung cancer and air pollution presents many of the same obstacles encountered in studying chronic respiratory diseases. The presence of multiple causes, dominated by smoking, and the existence of a long latency between initial exposure and the appearance of clinical disease head the list. In 1981, Doll and Peto suggested that a large case-control study of lung cancer be undertaken to evaluate the etiologic contribution of such factors as air pollution, passive smoking, and occupational exposures.[9] This is an important suggestion and deserves consideration with high priority.

The proposed case-control study would require perhaps 10,000 cases (some 140,000 new cases occur in the United States each year[1]) and a similar number of controls. Enough smokers and nonsmokers should be included for both independent and interactive effects of air pollution to be discerned. The cases and controls should form a nationally representative sample, so that results can be used to estimate the impact of air pollution on cancer throughout the country, rather than in one area. If the sample is geographically broad enough, it should be possible to avoid bias due to matching by residential area. Control over bias and confounding must be very tight; for instance, failure to distinguish cigarette use in detail might mean ignoring variations far more powerful in determining risk than exposure to air pollution. The chief limitation of the study, however, would lie in the degree of detail possible in the exposure histories, which will limit the study's ability to find small relative risks due to specific pollutants and large relative risks that affect only a small proportion of cases. But it should not prevent the study from providing reasonable estimates of attributable risk, that is, the proportion of cases due to air pollution. The answer to this question is invaluable, because it provides perspective for preventive efforts.

Other approaches to the study of air pollution and lung cancer are possible. Most prospective designs would fail, because of the relative infrequency of lung cancer in the general population. But the American Cancer Society is conducting its second massive prospective study of cancer in a cohort of 1.2 million persons; such an extraordinary cohort is large enough to detect small relative risks and yield actual incidence rates among the exposed groups while permitting adjustment for important confounders, such as smoking. The baseline interviews of the cohort have already been conducted. The initial questionnaire did not obtain information on the history of indoor or outdoor exposures outside the workplace. (Personal communication from S. Stellman, American Cancer Society) However, one question does identify those who have remained in the same residence for at least 10 years, and it could be used to define a nonmobile sample from whom histories of long-term residential exposures to air pollutants could be obtained. Even if only 5% of the entire cohort were so defined, that would amount to 60,000 long-term residents at risk of cancer for a followup period of 6 years. Thus, with relatively little investment, the American Cancer Society study could be modified to explore hypotheses relating lung cancer and air pollution. The time available for seizing this opportunity is short, though, inasmuch as the next biennial followup interview of the cohort is approaching and the total planned followup period for the study ends in 1990.

Many critics contend that traditional epidemiologic studies of cases of chronic disease are most limited by their after-the-fact, observational nature. It is true that these cases include some that might have been prevented; that is one reason why preclinical markers that point to an increased risk of developing lung cancer are of strategic interest. A variety of short-term laboratory tests have been developed to measure the interaction between environmental carcinogens and human genetic material in vivo. Most are performed on targets (such as peripheral lymphocytes and urinary nucleotides) that have only an indirect relationship to critical targets for lung cancer in bronchial cells. Others can measure the mutagenic potential of carcinogens in body fluids. Combinations of these tests could be applied to small cohorts that are well characterized with respect to patterns of exposure to air pollutants.

Evaluation of some of the short-term tests as variables for epidemiologic studies is urgently needed, to confirm that they measure what they intend to and adequately control for confounding and to determine what positive results mean with regard to disease risk. The need for this information varies according to the specific test. Laboratory studies are the most practical means of evaluation. Until predictive value is ascertained, the finding that a particular group or community exposed to air pollution has a higher prevalence of markers of genetic damage than some controls must be interpreted as a warning of potential risk.

EXPOSURE TO WOODSMOKE

"Does current exposure to woodsmoke cause or worsen acute or chronic respiratory disease, lead to acute or chronic changes in pulmonary function, or increase the risk of lung cancer?"

Descriptive studies that define the exposed populations and clarify the nature of woodsmoke exposures under various conditions should form an early part of the research strategy on this question. Ecologic studies comparing disease rates in communities with different patterns of wood use as fuel can be performed quickly and easily to form hypotheses and focus on populations at risk. Case-control studies like the one described in this chapter for acute bronchiolitis could easily incorporate information on woodstove use. The major thrust of the strategy, however, must be to establish cohorts exposed to woodsmoke for prospective study.

Selecting the exposure variables to be measured presents several choices. Categorical descriptors, such as hours of woodstove use per day or concentration of woodstoves in a neighborhood, must be developed. Indoor and outdoor source contributions to individual woodsmoke exposure must be distingusihed. Woodsmoke is a complex mixture, so various surrogates or index of exposure must be chosen. These could include benzo[a]pyrene, carbon monoxide, nitrogen oxides, or respirable particles. Each would have its own advantages, which would depend on the end points under study. Modifying factors--such as humidity, stove tightness, temperature fluctuations, and house ventilation--might have to be considered. If carcinogenicity is of concern, biologic markers of exposure, such as urine mutagenicity in the _Salmonella_/microsome assay or detection of DNA-benzo[a]pyrene adducts in nonsmokers, might prove useful. We should also note the recent appearance of a small passive monitor for polycyclic aromatic compounds. (Personal communication from Tuan Vo Dinh, Oak Ridge National Laboratory)

The effect measurements in woodsmoke studies could include symptom frequency, frequency of respiratory infection or asthmatic attacks, transient or persistent changes in lung function, changes in lung clearance, and markers of genetic damage in somatic cells. Reporting of acute respiratory symptoms in children might be particularly productive, as indicated by a recent study in Michigan.[11] The increase in the use of wood as a fuel in the United states has been relatively recent (except in some distinct populations, such as the Navajo Indians); that makes it difficult to assemble groups that had long-term exposure for studies of chronic effects, such as lung cancer. The greatest success could be achieved with small-panel, time-series studies.

The existence of communities (e.g., in New England and the Rocky Mountains) that have experienced rapid increases in the amount of woodsmoke pollution suggests some possibilities for fruitful studies, particularly if local ordinances lead to precipitous declines in exposure. Many populations in developing countries that use wood or other biomass as a primary fuel in village stoves have lived under conditions involving extraordinary exposure. A study of women cooks in central India measured total daily exposures to benzo[a]pyrene equivalent to the smoking of 20 packs of cigarettes a day. For several years, epidemic cor pulmonale (terminal heart failure usually due to lung damage) has been noted among young women in Nepal who work at cookstoves.[18] [19] [23]

These situations are difficult to compare with the U.S. experience, and the primary usefulness of studying them would be in determining whether there could be *any* possible associations between exposure and a given health effect and in validating biologic markers. The introduction of relatively simple and acceptable devices to reduce pollution from village cookstoves, such as chimneys and vents, would provide an excellent basis for health studies and at the same time take action on what is already perceived as a serious and nearly worldwide public health problem.[8]

The types of answers to be expected from foreseeable epidemiologic studies on woodsmoke are limited. Such studies are not likely to identify the specific components of woodsmoke responsible for an effect. But dose-response information for an index or surrogate of woodsmoke could be obtained, particularly in relation to acute health effects. Epidemiologic studies on this question should make it possible to weigh the importance of woodstove emission against that of other prevalent sources of exposure.

EXPOSURE TO NITROGEN DIOXIDE

"Does total exposure to nitrogen dioxide, from both indoor and outdoor sources, lead to or exacerbate acute or chronic respiratory diseases?"

It now appears that, except perhaps in a few selected areas, population exposures to nitrogen dioxide, NO_2, both average and peak, are determined primarily by emissions from unvented indoor combustion sources. Therefore, future studies must consider the joint impact of indoor and outdoor sources of this pollutant. Characterization studies will refine the understanding of the categorical descriptors of NO_2 exposure, but individual exposure monitoring of relatively small cohorts will still generally be necessary. Anchoring of aggregate exposure estimates in a larger cohort through intensive study of a selected sample is also possible. The appropriate monitoring equipment is available and awaits application in full-scale epidemiologic studies.

The frequency of respiratory infection is an important end point in NO_2 studies, to judge by the results of laboratory animal work. The role of NO_2 exposure in serious respiratory infections among infants has already been addressed in connection with the case-control study discussed early in this chapter.[27] Transient and persistent changes in lung function and symptom frequency are also of concern. In particular, new data on the effect of specific NO_2 sources on rates of lung growth in children need confirmation and expansion. As mentioned in Chapter 2, results of Japanese studies indicate that urinary hydroxyproline excretion might provide a useful early indicator of pulmonary connective-tissue degradation due to NO_2 exposure.[15] Further evaluation of the hydroxyproline marker in population studies involving high exposure is needed, to clarify the sources of variability in these measurements.

The development of categorical descriptors for NO_2 exposure (e.g., questions concerning kerosene-heater or gas-stove use that delineate exposure magnitude) will advance the testing of hypotheses regarding NO_2 and COPD in retrospective studies. The most precise data, however, will be gained through longitudinal studies of pulmonary function and measurement of individual exposures. Once again, studies on acute health effects should yield data that might eventually be used to identify a threshold exposure.

PERSISTENT EXPOSURE TO OZONE AND ACID AEROSOLS

"Does persistent exposure to ozone or acid aerosols (including sulfates) at high concentrations lead to an increased risk of developing chronic obstructive pulmonary disease?"

Average ozone concentrations remain high in some urban areas of the country and are rising in others where the density of automobile traffic has been increasing dramatically. As mentioned in Chapter 3, persistently high concentrations of acid aerosols (largely sulfur species) are being reported in some areas. Populations exposed to sulfates at annual average concentrations of 1 $\mu g/m^3$ to nearly 20 $\mu g/m^3$ can be identified, and they offer ample contrasts for study. There is a concern over the potential influence of these patterns of exposure on the risk of developing COPD. Results of long-term animal exposure studies support this possibility and a recent longitudinal study of an ozone-exposed cohort in Los Angeles pointed to decrements in pulmonary function among several age groups (unpublished manuscript, R. Detels, University of California, Los Angeles). The most important knowledge can now be gained by prospective cohort studies, which alone will have the capacity to describe exposure with the needed accuracy. That statement presupposes that specially designed air monitoring procedures will be relied on in lieu of routinely collected data. Personal monitoring of a sample of the cohort must also be used to determine the extent of misclassification error involved in the use of central, aggregate exposure data.

Cross-sectional studies, if large enough, will also be useful and should be derived automatically from baseline measures in longitudinal studies. Large cross-sectional studies of pulmonary function in long-term residents of polluted areas, compared with suitable controls, should be particularly useful. The availability of standard population values for pulmonary function that allow adjustment for smoking is a recent development of note (unpublished manuscript, A. Miller, Mt. Sinai School of Medicine). Exposures can be measured accurately only at or somewhat before the time of lung function measurement, so the impact of past and current exposures must be sorted out. Cohorts representing several different average exposures to ozone should be followed, including some with widely contrasting exposures. Optimal sample size, measurement precision, and control of nonrandom error must all be considered, to ensure the feasibility of such a study. Cohort size and followup time must be kept to a minimum, so that loss to followup, a crucial source of error in previous studies, can be restricted. Frequent contact with cohort members is also essential for this purpose.

EPISODIC EXPOSURE TO OZONE AND ACID AEROSOL HAZE

"Does episodic exposure to ozone or acid aerosols at high concentrations lead to excess morbidity from acute and chronic respiratory diseases?"

In addition to the problem of persistent exposure to ozone and acid aerosols, there is an emerging regional pattern of summertime "haze" episodes in the Northeast. These episodes are characterized by high concentrations of ozone and acid aerosol that are formed in the atmosphere and transported over wide geographic areas. Rural areas are affected by this phenomenon, and the highest seasonal variations in these pollutants might be found there. That suggests that a successful strategy might involve study of acute responses to ozone and acid aerosol during winter and summer in small cohorts of rural subjects. The most sensitive population imaginable would be exercising asthmatics, but any group likely to be outdoors and active during the haze episodes would be a reasonable study group. In fact, Lippmann and co-workers used such considerations in designing their study of transient lung function changes in children at rural summer camps in Pennsylvania and New Jersey.[14] Exacerbation of COPD in rural persons with this disease would also be an important topic for study, provided that likely exposures of persons remaining mostly indoors proved to be significant.

The regional episodic haze problem is also ideal for the use of epidemiologic surveillance networks. Once in place, these networks could detect increases in adverse health effects on the basis of hospital admissions, physician visits, or medication sales. During the summer of 1984, one haze episode resulted in 7 consecutive days of ozone above the national standard in the area from Philadelphia to New York. Morbidity surveillance was nonexistent, and mortality surveillance nearly so. The chief problem in such surveillance will be to separate out the effects of high heat and humidity, which invariably accompany these polluted air masses.

The potential chronic effects of episodic ozone and acid aerosol will remain more difficult to study, in part because of the relatively recent appearance of the pollution pattern and because of the difficulty involved in separating persistent from episodic exposures. Again, rural areas that generally have low exposure to ozone and primary acid aerosol, except during the summer, might be preferable sites for studies. Persons without air conditioning who spend much time outdoors would be receiving the highest exposures. It might be feasible to couple the summertime acute studies on children with wintertime followup of the same children over a period of 2-3 years. The expense of establishing a new cohort could thus be reduced, exposures to the pollutants in the summer verified, and the acute-study measurements used as a baseline for observation of the rate of growth in pulmonary function.

Given careful planning and adequate time and funding, currently available epidemiologic techniques could establish the acute impact of summertime excursions in ozone and acid aerosol on sensitive populations.

EXPOSURE TO RADON

"Does exposure to radon and its progeny at current indoor concentrations increase the risk of developing lung cancer?"

A survey of radon concentrations in soil, water, and indoor air in various parts of the United States would assist the development of an epidemiologic strategy on this question in several ways. First, although several areas with relatively high radon concentrations in buildings have already been identified, increasing the list would expand the options for selecting study populations and determine the potential size of the population at risk. For example, a national survey in Sweden has sampled radon concentrations in approximately 50,000 dwellings.[24] Second, comparable data on radon concentrations in numerous areas might be used in a preliminary ecologic analysis that combines radon exposure data with local data on lung cancer mortality. Third, if some descriptive studies were detailed enough, useful information on factors influencing the entry, exit, and transformation of radon in buildings could be generated. This would sharpen the focus in assigning groups or individuals to exposure levels and provide better categorical descriptors of exposure for questionnaires. For example, it has recently been demonstrated that radon progeny readily attach to particles found in cigarette smoke, thereby increasing and prolonging the effective dose experienced by both active and passive smokers.[5]

In addition to descriptive studies, case-control studies of lung cancer in areas with wide contrasts in radon exposure would be feasible. Relatively large numbers of cases would be required for adequate statistical power, because the risk is probably low, compared with that associated with smoking. Natural experiments, in which exposures within a community vary sharply according to the specific location of a house or the use of a different water supply or building materials, should be actively sought. One such study, comparing residence in wood versus stone houses, has already been conducted in Sweden.[3] Aside from such geographically focused studies, information on radon and lung cancer might be derived from the large-scale case-control study or prospective studies mentioned earlier in connection with lung cancer. Such information will not be very substantial, because reliable means for evaluating exposure of such large, heterogeneous populations are still lacking.

Cohort studies of uranium miners and other types of miners have successfully demonstrated that radon and its progeny can cause lung cancer in humans. However, the least-exposed miner group that showed a significant excess of lung cancer still had cumulative lifetime exposures at least several times higher than that likely to be experienced by residentially exposed persons.[17] Cohort studies (either prospective or historical-prospective) of residential exposure are therefore not likely to be large enough to detect the potential excess risk involved, unless short-term measures of risk that occur more frequently (such as markers of genotoxicity) are used. Sputum cytology analysis has been positive in studies of uranium miners[2] and could be clinically useful for screening these men, but morphologic abnormalities in exfoliated cells might occur so late as to have almost the same frequency as lung cancer itself. Chromosomal aberrations in peripheral blood lymphocytes, however, have also been observed in radon-exposed miners and in one study of home exposure and might prove to be a useful end point for residential cohort studies.[7] [28]

Radon has decreased in mines in recent decades, and many miners' long-term exposures are now comparable with those of persons in some kinds of dwellings. Furthermore, some homes have been shown to exceed the permitted occupational radon concentration. The current followup of miners, if done carefully and with large enough cohorts, should be supported, to estimate risks in this dose range. Recent work in dose modeling has clarified some of the factors (including dust concentrations) involved in extrapolating radon dosage from the mine environment to the home.[10]

The most useful direct approach to the radon-lung cancer question is through the case-control method, so exposure measures will most often be retrospective and hence subject to considerable uncertainty. Nevertheless, radon sources are relatively stable emitters, and, assuming that changes over the years in exposure-modifying factors (such as the sealing of buildings) can be accounted for, retrospective estimates of exposure of long-term residents to radon are likely to be more accurate than those of exposure to most other air pollutants. Estimation of rough dose-response relationships should be possible, if a positive association can be found. The accuracy of such estimates will depend heavily on how well local exposure conditions have been characterized. Questions of attributable risk and interactive effects with smoking are important and should be addressed in these studies.

REFERENCES

1. American Cancer Society. 1985 Cancer Facts and Figures, p. 8. Publication No. 5008-LE. Washington, D.C.: American Cancer Society, 1985.

2. Auerbach, O., G. Saccomanno, M. Kuschner, R.D. Brown, and L. Garfinkel. Histological findings in the tracheobronchial tree of uranium miners and non-miners with lung cancer. Cancer 42:483-489, 1978.

3. Axelson, O., C. Edling, and H. Kling. Lung cancer and residency: A case referent study on the possible impact of exposure to radon and its daughters in dwellings. Scand. J. Work Environ. Health 5:10-15, 1979.

4. Bates, D.V., and R. Sizto. Relationship between air pollutant levels and hospital admissions in Southern Ontario. Can. J. Pub. Health 74:117-122, 1983.

5. Bergman, H., C. Edling, and O. Axelson. Indoor radon daughter concentrations and passive smoking, pp. 79-84. In B. Berglund, T. Lindvall, and J. Sundell, Eds. Indoor Air. Stockholm, Sweden: Swedish Council for Building Research, 1984.

6. Berry, G. Longitudinal observations: Their usefulness and limitations with special reference to the forced expiratory volume. Bull. Physio-pathol. Respir. 10:643-655, 1974.

7. Brandom, W.F., G. Saccomanno, V.E. Archer, P.G. Archer, and A.D. Bloom. Chromosome aberrations as a biological dose-response indicator of radiation exposure in uranium miners. Radiat. Res. 76:159-171.

8. DeKoning, H., K.R. Smith, and J.M. Last. Biomass Fuel Combustion and Health. Report No. EFP/84.64. Geneva: World Health Organization, 1984.

9. Doll, R., and R. Peto. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J. Nat. Cancer Inst. 66:1191-1308, 1981.

10. Harley, N.H., and B.S. Pasternak. A model for predicting lung cancer risks induced by environmental levels of radon daughters. Health Physics 40:307-316, 1981.

11. Honicky, R.E., S. Osborne, III, and C.A. Akpom. Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. Pediatrics 75:587-592, 1985.

12. Kitagawa, T. Cause analysis of the Yokkaichi asthma episode in Japan. J. Air Pollut. Control Assoc. 34:743-746, 1984.

13. Lebowitz, M.D. Smoking habits and changes in smoking habits as they relate to chronic conditions and respiratory symptoms. Am. J. Epidemiol. 105:534-543, 1977.

14. Lippmann, M., P.J. Lioy, G. Liekauf, K.B. Green, D. Baxter, M. Morandi, B. Pasternak, D. Fife, and F.E. Speizer. Effects of ozone on the pulmonary function of children, pp. 423-446. In M.A. Melman, S.D. Lee, and M.G. Mustafa, Eds. Advances in Modern Environmental Toxicology. Vol. V. Princeton, N.J.: Princeton Scientific Publishers, 1983.

15. Matsuki, H., F. Osaka, H. Kasuga, and M. Sugita. Epidemiological study on the effects of smoking and air pollution using urinary hydroxyproline: creatinine ratio on the healthy schoolchildren and adults. Jap. J. Pub. Health 28:505-515, 1981.

16. Mitchell, E.A., and D.R. Cutler. Pediatric admissions to Auckland Oospital for asthma from 1970 to 1980. New Zeal. Med. J. 97:67-70, 1984.

17. National Research Council, Committee on Indoor Pollutants. Indoor Pollutants. Washington, D.C.: National Academy Press, 1981. 537 pp.

18. Pandey, M.R. Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal. Thorax 39:337-339, 1984.

19. Pandey, M.R. Prevalence of chronic bronchitis in a rural community of the Hill Region of Nepal. Thorax 39:331-336, 1984.

20. Pohl-Ruling, J., and P. Fischer. The dose-effect relationship of chromosome aberrations to α and γ irradiation in a population subjected to an increased burden of natural radioactivity. Radiat. Res. 80:61-81, 1979.

21. Samet, J.M., I.B. Tager, and F.E. Speizer. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am. Rev. Respir. Dis. 127:508-523, 1983.

22. Schlesselman, J.J. Planning a longitudinal study: II. Frequency of measurement and study duration. J. Chron. Dis. 26:561-70, 1973.

23. Smith, K.R., A.L. Aggarwal, and R.M. Dave. Air pollution and rural biomass fuels in developing countries: A pilot village study in India and implications for research and policy. Atmos. Environ. 17:2343-2362, 1983.

24. Swedjemark, G.A. Indoor measurements of natural radioactivity in Sweden. SSI 1979-026. Stockholm: National Institute for Radiation Protection, 1979.

25. U.S. Department of Health and Human Services. Chronic bronchitis, white females, 1965-1971. In T.J. Mason, J.F. Fraumeni, Jr., R. Hoover, and W.J. Blot, Eds. An Atlas of Mortality from Selected Diseases. NIH Publication No. 81-2397. Washington, D.C.: U.S. Department of Health and Human Services, National Institutes of Health, 1981.

26. U.S. National Center for Health Statistics. Detailed Diagnosis and Surgical Procedures for Patient Discharge from Short Stay Hospitalization. Publication No. (PHS) 85-11743. Hyattsville, Md.: U.S. Department of Health and Human Services, National Center for Health Statistics, 1984. 278 pp.

27. Ware, J.H., D.W. Dockery, A. Spiro, III, F.E. Speizer, and B. G. Ferris, Jr. Passive smoking, gas cooking, and respiratory health of children living in six cities. Am. Rev. Respir. Dis. 129:366-374, 1984.

Chapter 6

Conclusions and Recommendations

6

CONCLUSIONS AND RECOMMENDATIONS

The Committee reviewed the current status of epidemiologic research on air pollution in the United States. It sought to identify the types of epidemiologic activities that could feasibly be applied to determine the size and nature of the health risks of air pollution, given current magnitudes and patterns. It observed that new approaches will be needed to quantify adverse health effects associated with low concentrations of air pollutants and to separate the impacts of individual pollutants more effectively.

The Committee concluded that efforts to specify current and future research questions have been insufficient and that additional investment is needed in research on and development of appropriate investigative tools. It expects the development of new techniques and strategies to make it possible to overcome some of the barriers to the application of epidemiologic approaches. The Committee also concluded that many previous studies had generally failed to recognize the complexity of air pollution research and to integrate all the relevant sciences, including epidemiology, into coherent research plans and programs.

The Committee finds that current air pollution can cause acute and perhaps chronic health effects, particularly respiratory effects, in the population of the United States. Respiratory disease is a major cause of work loss and disability. Even though exposure to some major types of pollution has decreased substantially in the last 15 years, exposure to other types has persisted. Improvement has not been uniform in all parts of the country, and some new patterns of air pollution are emerging. The entire population is affected by low concentrations of both indoor and outdoor air contaminants. Even if only a small proportion of very prevalent disease is due to air pollution, the absolute amount of illness that could be prevented by reducing air pollution would be large.

Epidemiologic studies can be used to accomplish several things that cannot be accomplished in other ways:

- Directly determine whether a public health problem exists.

- Estimate the magnitude of the existing public health problem.

- Evaluate the impact (health and economic) of decreases in exposure.

- Define characteristics of the problem that can guide intervention even before mechanisms are understood.

The results of well-conducted epidemiologic research are important in the development and revision of air quality standards and other means of regulating air pollution. It is recognized, however, that regulatory decisions sometimes have to be made before complete observational evidence is available. Although regulatory requirements must influence the definition of research questions and the design of studies, they should not be the sole basis for the development of broad research programs. Regulatory concerns, when narrowly interpreted, revolve around identification of "safe" exposures to individual pollutants--a question that presents few opportunities for studies of their effects on free-living populations. The Committee concludes that epidemiology, if it addresses this question and others mentioned above, can make a unique contribution to the prevention of illness related to air pollution.

In view of the above conclusions, the Committee offers the following major recommendation:

The Environmental Protection Agency should develop a long-term plan for research on air pollution; and population-based studies, in the form of a program in epidemiology, should be an integral part of that plan.

CHARACTERISTICS OF A PROGRAM IN AIR POLLUTION EPIDEMIOLOGY

To be productive and cost-effective, the epidemiologic program should have the following four major characteristics:

- Maintenance of a capability to interpret and synthesize current knowledge about air pollution and, accordingly, to plan relevant short-term epidemiologic research and make appropriate changes in long-term research.

- Inclusion of mechanisms for the creation of multidisciplinary teams to plan and conduct population-based epidemiologic research on the adverse health effects of air pollution.

- Means of ensuring stable, long-term epidemiologic research in a context that supports the career development of the researchers and thus limits disruptive changes in personnel.

- Exploration of collaboration with agencies that collect or could collect relevant data, after careful consideration of overall long-term data needs.

A productive epidemiologic research program must have a dual character with respect to sensitivity to outside forces. Part of the program must be dedicated to responding to rapidly changing conditions that offer important opportunities for study, to the varying concerns of regulators, and to new information from technologic development and parallel disciplines. In particular, advances in toxicology and clinical research, and epidemiology should be parts of the same framework; advances in any one can drive new efforts in the others. Another part of the program, engaged in long-term research strategies or longitudinal studies, must remain relatively isolated and free from abrupt change, although the incorporation of new elements will sometimes be desirable.

It is important that the Environmental Protection Agency (EPA) program staff at all levels include highly trained and experienced epidemiologists, regardless of whether research is conducted intramurally or extramurally. Continuous access to both advice and review from scientists outside the institution will also be greatly needed.

Given the constraining and difficult nature of today's questions about air pollution, stable research teams with expertise in several critical fields will be most productive. Epidemiologists in the teams should collaborate with atmospheric scientists, statisticians, and health effects scientists in all phases of research, from study design through interpretation. The present structure of many universities and government research agencies often makes it difficult to arrange such collaboration. Financial and administrative mechanisms that encourage development of these teams must be implemented; and the EPA program staff itself must have a multidisciplinary composition.

The value of large data systems developed for reasons other than air pollution studies (such as the National Health and Nutrition Examination Survey, the National Health Interview Survey, and the National Ambulatory Medical Care Survey) as resources in air pollution research should be assessed. Whether modifications in some of them and linkage to air pollution exposure data constitute a feasible and cost-effective research approach that affords very large samples should also be explored. Modification in the routinely collected air sampling data alone might be appropriate, to facilitate use of these data in some types of epidemiologic studies.

THE FOCUS FOR RESEARCH

For the immediate future, the epidemiologic research program should focus on the following exposures and effects of concern:

- Persistent air pollution problems, including the health effects of acid sulfate particles, ozone, nitrogen dioxide, carbon monoxide, lead, and radon. It should be flexible enough to address emerging problems, such as the health effects of products of incomplete combustion and volatile organic chemicals.

- Lung disorders in which air pollution might play a role, including chronic obstructive pulmonary disease, asthma, decreased rate of lung growth or increased rate of lung decline with aging, and increased susceptibility to acute respiratory infections.

- The quantitative contribution of air pollutants to lung cancer in human populations. For this purpose, it could take advantage of the existing funding arrangement between EPA and the National Cancer Institute for the support of epidemiologic studies of this problem.

Many important questions about the "traditional" pollutants remain unanswered. For example, the acute and chronic respiratory effects of acid aerosol and ozone exposures, which might result only from outdoor sources, are not well understood. An extensive population, perhaps in excess of 100 million, is exposed to ambient ozone at high concentrations during the spring and summer. Shifts in coal combustion to the south central states will result in an increase in the area and population exposed to acid aerosols. No systematic epidemiologic study has been designed to assess either the acute or chronic effects of this type of shift in exposure. Exposures to acid aerosols are likely to increase more in rural areas than in urban areas, so it is recommended that consideration be given to locating baseline and followup studies in rural areas.

As new automotive fuels, new industries, new fuel sources, new commercial products for the home, and new building ventilation patterns are introduced, they might yield new pollutants and pollution patterns that require epidemiologic evaluation. These changes will result in increased exposures to volatile and particulate organic compounds, radon, carbon monoxide, and other potentially hazardous materials.

Indoor air pollution can be a major factor--in some instances the principal factor--in determining total personal exposure (averaged and acute) to air pollutants. Epidemiologic studies must therefore consider indoor or outdoor concentrations, or both, depending on the health response and pollutant being examined. For example, average and peak exposures to nitrogen dioxide are determined primarily by the presence of unvented indoor combustion sources. Peak exposures higher than those in most urban outdoor environments occur often in residences that use unvented gas or kerosene as a cooking or heating fuel. Therefore, to assess the health effects of nitrogen dioxide, EPA should study respiratory infection, pulmonary function changes, and, as soon as possible, biochemical indicators in association with indoor exposures and simultaneous outdoor exposures.

There have been important advances in air monitoring instruments and inferential data analysis techniques. Air pollution is a complex mixture of gases, vapors, and particles; epidemiologic studies will often benefit from detailed characterization of its components. For instance, the chemical composition and acidity of size-fractionated particles should be characterized where appropriate. In some cases, new techniques for biologic characterization are also appropriate. Detailed characterization can help to determine the air pollution components most closely associated with health outcomes, potential confounders, and the relative contributions of various sources.

The most readily observed health effects of air pollution are in the respiratory system. The proportion of the overall disease burden from common respiratory diseases that is attributable to air pollution has not yet been established. This part of the disease burden includes both the development of disease de novo and the exacerbation of pre-existing disease.

Air pollution might have nonrespiratory effects that, although not emphasized in this report, also deserve study. These include neurobehavioral deficits and essential hypertension related to lead exposure, ischemic heart disease related to carbon monoxide, and carcinogenesis and mutagenesis related to various volatile hydrocarbons.

Respiratory cancers, which are the most common cause of cancer death in men and will soon be in women, are attributable largely to cigarette smoking. However, attempts to assign proportions of this disease burden to separate causal agents, such as air pollution, are frustrated by the multifactorial and interactive etiology of these cancers. It is particularly important to understand the role of air pollutants in lung cancer, inasmuch as interactive effects might multiply the number of cases that could be prevented by reducing exposures.

The limits of an epidemiologic research program depend on the questions under consideration. Only by considering each research question carefully can one understand the limits of investigative methods and discuss them productively. In general, studies of chronic health effects are more difficult than studies of acute effects. Specific reasons have been discussed in the preceding chapters; they include uncertainties in measurements of long-term exposure, the relative rarity of chronic diseases (which strains statistical power), and limitations in our understanding of the biology underlying the gradual evolution of chronic damage. Epidemiologic studies can show whether exposure to a complex pattern of polluted air increases the risk of adverse health effects in human populations, but studies are often limited in their ability to delineate the quantitative relationships between concentrations or sources of specific air pollutants and health. Such delineation requires interpretation of epidemiologic data in conjunction with toxicologic and clinical research.

Susceptibility to the effects of air pollution varies widely; studies that focus on sensitive subgroups, necessary in themselves, are an important part of strategies to detect and measure the effects of air pollution in the general population. The sensitive-subgroup approach to increasing the effectiveness of air pollution epidemiology must be furthered by broad-based efforts (toxicology, clinical research, and epidemiology) to clarify the precise nature and degree of sensitivity of such groups as the young, the elderly, those with increased airway reactivity, and those with particular pre-existing diseases. Opportunities for carrying out epidemiologic studies on populations exposed to unusual magnitudes or patterns of air pollution must be specifically sought. By circumventing various methodologic constraints, these studies might provide information that would not otherwise be easily obtained. The opportunities include the use of occupational cohorts exposed to high concentrations, groups living in pristine environments or in highly polluted environments, and groups subjected to marked temporal changes in pollution. Collaboration with researchers in other countries might be necessary.

NEW RESEARCH TOOLS AND OPPORTUNITIES

Some constraints in air pollution epidemiology could be removed by complementary research to develop and explore the application of new tools for measuring exposure and effect. Such research and development is especially needed in two categories:

- New methods for assessing personal exposure and response to air pollution to be selectively incorporated into epidemiologic studies, with attention to the cost-effectiveness of these methods.

- Epidemiologic studies designed to determine the characteristics and the predictive value of potentially useful physiologic, biochemical, and morphologic markers of subclinical effects.

Personal exposure monitoring and modeling are sometimes useful in epidemiologic research in defining study populations, optimal sample sizes, relationships of surrogate measures to exposures, and the extent of exposure misclassification associated with the use of central monitoring data. Depending on the design of a given study, only a sample of the study population might require such detailed monitoring; various strategies need to be explored and their performance documented.

Markers of physiologic, biochemical, and cellular morphologic changes will be increasingly important in air pollution studies. FEV_1, a physiologic test of lung function, has been used successfully to measure differences related to air pollution between populations. Serial measurement of FEV_1 has also proved to be sensitive and effective in following the growth and decline of lung function in large populations. In adults, a more rapid than normal decline in FEV_1 predicts premature death from pulmonary failure. Although FEV_1 is a simple and highly reproducible test, its interpretation in terms of organ or cellular pathology is complex and subject to some judgment.

Some biochemical indicators of air pollutant exposure or early effects--such as blood lead and carboxyhemoglobin concentrations, urinary mutagens, and indexes of genotoxic damage--have already been successfully applied in population studies. Other biochemical indicators, designed to detect early pathologic processes in the lung, have recently shown promise and require further development and validation. Insights into the pathogenesis of emphysema have been particularly fruitful in opening possibilities for biochemical markers related to the breakdown of connective tissue in the lung. Development of biochemical markers for epidemiologic studies requires particular attention to constraints imposed by the need to study large groups of relatively healthy people.

Appendixes

APPENDIX A

MORBIDITY AND MORTALITY ASSOCIATED WITH ACUTE AND CHRONIC RESPIRATORY DISEASE IN THE UNITED STATES

TABLE A-1

Morbidity (1981) and Mortality (1983) Associated with Acute Respiratory Diseases in the United States[a]

Conditions	Acute Conditions per Person[b]	Total Days Restricted Activity per Person	Bed Disability Days per Person	Days Lost from School per Child (Age 6-16)[c]	Days Lost from Work per Person (17 and Over)[c]	Deaths (1983)[c]
All acute conditions	2.12	9.59	4.19	4.36	3.37	NA
Total acute respiratory conditions	1.12	4.03	2.11	2.53	1.41	NA
Pneumonia	0.015	0.238	0.144	NA	NA	52,220
Influenza	0.50	1.9	1.15	1.20	0.764	1,370
Bronchitis	0.028	0.172	0.088	NA	NA	NA
Upper respiratory conditions	0.56	1.60	0.672	1.14	0.459	NA

---

[a] Source: Morbidity data from the National Center for Health Statistics, National Health Interview Survey: United States, 1981. DHHS Publication No. (PHS) 82-1569. Only conditions that limited activity or required medical care are counted. Mortality data from NCHS Vital Statistics Report 32:19, September 21, 1984.

[b] Children under age 6 averaged 3.80 acute conditions per year, 1.99 of which were respiratory.

[c] NA = not available.

TABLE A-2

Morbidity (1979-1981) and Mortality (1983) Associated with Chronic Pulmonary Conditions in the United States[a]

Chronic Pulmonary Conditions	Prevalence (No. Persons Affected)[b]	Persons with Major Limitation of Activity[c]	[illegible] of Restricted [illegible]ivity per Condition	Bed-Days per Condition	Deaths (1983)
Chronic bronchitis	7.8 million	0.28 million (3.8%)	9.5	3.2	3,480
Emphysema	2.2 million	0.98 million (44%)	42.5	13.4	13,250
Asthma	6.8 million	0.89 million (13%)	16.3	5.6	3,440
Total COPD[d]	NA	NA	NA	NA	66,340

---

[a] Source: Unpublished morbidity data from the National Center for Health Statistics, National Health Interview Survey, 1979-81. Mortality data from NCHS Vital Statistics Report 32:19, September 21, 1984.

[b] Some persons might be counted as having more than one of these conditions.

[c] Percentages are proportions of affected people who had major limitations of activity.

[d] Including chronic bronchitis, emphysema, asthma, and deaths coded nonspecifically as COPD. NA = not available.

APPENDIX B

NATIONAL AMBIENT AIR QUALITY STANDARDS

TABLE B-1

Current National Ambient Air Quality Standards[a]

Pollutant	Concentration	Comments
Sulfur dioxide (SO_2)	80 µg/m^3 (0.03 ppm)	Annual arithmetic mean
	365 µg/m^3 (0.14 ppm)	Maximum 24-hour concentration not to be exceeded more than once per year
Total suspended particulates (TSP)	75 µg/m^3	Annual geometric mean
	260 µg/m^3	Maximum 24-hour concentration not to be exceeded more than once per year
Carbon monoxide (CO)	10 mg/m^3 (9 ppm)	Maximum 8-hour concentration not to be exceeded more than once per year
	40 mg/m^3 (35 ppm)	Maximum 1-hour concentration not to be exceeded more than once per year
Ozone (O_3)	235 µg/m^3 (0.12 ppm)	Not more than one day per calendar year with maximum hourly average concentrations above 235 µg/m^3
Nitrogen dioxide (NO_2)	100 µg/m^3 (0.05 ppm)	Annual arithmetic mean (generally monitored continuously)
Lead	1.5 µg/m^3	Maximum arithmetic mean averaged over a calendar quarter (frequently monitored weekly)

---

[a] Reprinted from Code of Federal Regulations, Title 40, Part 50, 1984.

APPENDIX C

PITFALLS IN DESIGN, ANALYSIS, AND INTERPRETATION

This appendix provides detail on some of the basic issues involved in the design, analysis, and interpretation of contemporary epidemiologic studies on air pollution.

BIAS, CONFOUNDING, AND CHANCE

The three most formidable influences on study validity are bias, confounding, and chance.

BIAS

Bias is the consequence of any technique used in a study that produces results that tend systematically to be on one side or the other of "true" values. It is sometimes referred to as systematic or nonrandom error. Random error, in contrast, falls equally on both sides of true values. Bias can arise during any phase of study activity--design, data collection, analysis, or interpretation. Texts and review articles describe the many types of bias that epidemiologists have identified.[12]

Chapters 2 and 3 provide the basis for an understanding of biases that arise from the improper assessment of either exposure or effect. An instrument used for measurement, such as a questionnaire or a sampling device, obviously can produce a systematic error. In air pollution research, far more serious biases are likely to result from improper understanding (or "modeling") of exposure or effect, which can also produce estimates for individual subjects that are consistently too high or too low. For instance, an acute effect might be underestimated if the influence of concurrent respiratory infection is ignored or the appropriate lag time between exposure and response is miscalculated. Ozone exposure might be systematically overestimated for a person who spends all day in an air-conditioned building.

The major practical impact of bias is the misclassification of study subjects with respect to the extent of exposure, the effect, or both. Whether biases in the data lead to overestimates or underestimates of risk depends on how these classification errors are distributed among groups that are assumed to have various exposures. If there is a tendency to assign greater values to effects in subjects with greater exposure, misclassification can increase the likelihood of a false-positive result, or overestimation of risk. If there is a tendency to assign lower values to effects in subjects with greater exposure, misclassification can increase the likelihood of a false-negative result. Finally, if the degree and direction of the bias in measurement are indifferent to the presumed magnitude of exposure, subjects will be randomly misclassified. In the latter case, what is a nonrandom error on the level of individual measurement behaves like a random error at the level of population measurement. The net effect will be a bias toward negative studies or underestimation of risk, because the real contrasts between exposure groups in the study will be diluted, black and white will become gray, and the magnitude of the association between exposure and effect will be underestimated--or the association might disappear altogether. A true relative risk of 12 (risk of disease in exposed group is 12 times risk in nonexposed or less-exposed group) might be estimated as a relative risk of 2. In air pollution studies, where true relative risks tend to be rather low, a relative risk of 2 could disappear.

It is clearly preferable to eliminate or reduce bias during the design phase, but, with proper planning, it can sometimes be estimated (even after data collection), and its potential distortion of study results assessed. The techniques for measuring some types of bias include focused substudies (e.g., comparison of telephone interviews with a subsample of personal interviews), use of multiple control groups (e.g., comparison of lung-cancer cases with both other-cancer and noncancer controls), and comparison of baseline data on subjects lost to followup with those on persons followed up.

CONFOUNDING

Confounding variables are factors that vary with exposure and are causally related to the outcome of interest. They can vary directly or inversely with exposure, and the causal relation can be positive or negative.

The net impact of a confounding variable on a study's result is determined by the direction and magnitude of its associations with exposure and effect. Cigarette smoking, for example, is usually positively correlated with exposure to ambient air pollution exposure (heavier smokers tend to live in more polluted areas) and to many forms of respiratory illness.[9] Failure to control for the effects of cigarette smoking will tend to produce a false or spurious association between air pollution and illness. Other uncontrolled confounders can interfere with the detection of a true association. Confounding can ultimately be viewed as a form of bias in which, by definition, errors are unevenly distributed among exposure groups. In a specific study, this bias might cause either a false-positive or false-negative result.

Epidemiologists use three basic techniques to control for the impact of confounding variables or unevenly distributed biases. First, study populations can be selected so as to reduce or avoid these factors. For example, a study of lung cancer in nonsmokers or a study of lung function in young children would completely avoid confounding by cigarette smoking; a study conducted in a nondeveloped country might avoid biases due to air conditioning. Second, matching or stratification can be used during the design phase to make the prevalence of a confounding variable similar among groups to be compared. Third, when data have been collected, subjects can be analyzed in groups stratified by particular characteristics, such as age or smoking, or the effect of confounding can be adjusted for with multivariate analysis .

CHANCE

Epidemiologists must be sensitive to the role of chance in influencing the results of a study. Chance operates in several fundamentally different ways, of which the most important are sampling error (choice of subjects), random error in measuring exposure or effects, and random error of inference regarding overall study results.

Some random error in measuring exposure, effect, or a confounding variable is unavoidable, even with the most precise instruments. To minimize it, we can increase the precision of the instrument or take more samples so that the average measurement more closely approaches the truth. Random error does not constitute a dominant problem in air pollution epidemiology, compared with the problems presented by nonrandom errors.

There is always some probability that the results of a given study are due substantially to chance (sampling variability). The field of statistics has developed a set of techniques for estimating and expressing this probability. First, if the result of a study is negative, the probability that this result is due to chance alone is assessed by calculating the study's statistical power. The higher the statistical power, the smaller the likelihood of a false-negative result--i.e., the more likely that the lack of an effect is genuine.

Power is a function of sample size, magnitude of the association sought, and prevalence of exposure in the study populations. It is important to note that statistical power, as conventionally thought of, is not affected by nonrandom error, so a very "powerful" study could be insensitive because of nonrandom errors in the data.

Power can be calculated after a study to assess the validity of a negative result. But it must be considered during study design. The values of parameters of a power calculation can be estimated during study planning, and the minimal sample needed to detect an effect of a given size with acceptable certainty can be determined. The calculations must take into account the need for adequate numbers of individuals within critical groups in the population; the numbers must be large enough to allow stable rates and average values for each group, whether defined by race, sex, day of testing, or extent of exposure. In some instances, the sample size will be fixed in advance or have an upper limit, because of the established number of persons in an exposed cohort or of cases available for study. By definition, exposure to ubiquitous air pollutants is widespread, and the size of the exposed population is rarely a major constraint.

Matters of power and sample size should be explicitly addressed during the design phase, both to make it possible to terminate planning of work that has little likelihood of success and to ensure that negative findings, if they occur, will be properly interpreted. Some negative findings, of course, are of great value and should be pursued with vigor (and large samples).

The likelihood that a positive study result could be due to chance alone is usually estimated by calculation of the statistical significance, or the *p* (probability) value. The *p* value reflects the effects of both random error and nonrandom error (bias), but statistical theory (as well as tabulations of critical cutoff values) assumes that only random error is present. Consequently, calculation of *p* values explores only a part of the real likelihood that a particular study result is due to chance. The wider use of confidence intervals instead of *p* values in reporting the results of air pollution research would add useful information about the size, direction, and certainty of any departure from the null hypothesis. Several reviews of the generic problems involved in using *p* values are available. It suffices here to say that future air pollution studies will benefit from the recognition that statistical significance is far easier to calculate than it is to interpret.

GROUP DATA VERSUS INDIVIDUAL DATA

A critical part of study design involves decisions as to whether individual exposures and individual outcomes will be estimated or will be available only in aggregated form (e.g., by family, by city block, or by community). Aggregation, or grouping of data on individuals, generally reduces the sensitivity of a study design. When a group of individuals have been assigned to a given exposure or effect category, important variations among them are obscured and information is lost. Lack of awareness of the individual variation can lead to misclassification; for instance, some members of a group with small average exposure might actually have had moderate or large individual exposures. In air pollution studies, this problem occurs typically when exposure data from central stations, rather than individual monitors, are used.

As pointed out in Chapter 3, individual or personal monitoring is not feasible or necessary in every study. Some studies, designed to answer very important questions, require large numbers of people. Cohort studies designed to provide data on the effect of ambient air pollution on changes in pulmonary function over time are an example. Even larger populations must be studied if the health outcome variable is a morbidity event. Such events as hospital admissions for asthma, although common in a medical context, are relatively rare among the population as a whole. Therefore, one has to observe a very large population, if one is to detect an impact of air pollution on the number of these events within a reasonable period. The Ontario Air Pollution Study, for example, detected a daily excess of 22 asthma admissions due to air pollution among nearly 6 million exposed and observed people.[1] The large population studied provided the needed statistical power, but also dictated the use of aggregate, rather than individual, exposure data. This tradeoff between cohort size and precision of information is unavoidable. Both small-cohort and large-cohort studies are needed, because they provide answers to fundamentally different research questions.

If personal monitors are available and sufficiently accurate and if the cost of their maintenance does not require reductions in sample size that outweigh gains in statistical precision, they can be quite valuable even in large-cohort studies. Personal monitoring can verify and "anchor" the aggregated measurements from central monitoring stations in the community. If serious discrepancies appear between personal-monitor data and central data, one can try to reconcile them and determine the causes and extent of misclassification errors. If this kind of work is done during a pilot study, it can also help to determine the sample size required in the definitive study. Deviation of individual exposure from aggregate exposure might be critical when effects are nonlinear. Consider, for example, a case in which the centrally measured value is just below some threshold, but some persons have had exposures substantially higher or lower than the average. Personal monitoring of every subject is not required for these purposes; a subsample might be sufficient.

Although the unnecessary aggregation of data is undesirable, aggregate data are in some ways the preferred type of epidemiologic data for prevention and "community diagnosis." Aggregate data on indexes of respiratory health allow us to compare the health of one community with that of another and to assess the community-wide impact of preventive strategies. Moreover, ambient air pollution is regulated on the basis of aggregate data on exposure. Consequently, epidemiologic studies that use such data are directly interpretable in relation to national air quality standards.

SOURCES OF RANDOM VARIATION

Epidemiologic studies of air pollution must be designed with an awareness that random variation can have many sources and that individual observations are often not fully independent. For example, a study of respiratory symptoms in 50 subjects in each of two cities recorded once a month for a year might be regarded as having a sample size of 1,200 (observations) or 100 (subjects) or 2 (cities). If results are to be used to characterize other cities that vary appreciably in important ways, the relevant sample size might be closer to 2 than to 100 or 1,200. When such considerations are apparent during the design of a study, the distribution of observations allowed by the study budget can be adjusted (e.g., 10 subjects in each of 10 cities, rather than 50 in each of two). There is generally no substitute for adequate sampling and study of each potentially relevant source of random variation, such as city.

A common design in air pollution epidemiology involves a comparison of respiratory health in a "polluted" town with that in one or two less polluted or unpolluted towns. The pairs of towns compared are assumed to be representative of all similar pairs of towns with similar contrasts in pollution. That assumption is not necessarily valid, inasmuch as the next two or three pairs, selected at random from those with identical pollution contrasts, might yield different associations between air pollution and health. The selection of towns or groups for comparison is thus a source of random variation distinct from the random variation related to selection of individual subjects. Small sample size for this group component of variation can increase the uncertainty attached to a study's results and limit generalization from them. For that reason, a recent large epidemiologic study of air pollution in France used aggregate exposure data for study subjects scattered throughout 28 towns or districts.[3]

SELECTION OF STUDY POPULATION AND ROLE OF SENSITIVE POPULATIONS

Study subjects are ordinarily selected because they are exposed to air pollution of different magnitude or because they do or do not have some outcome of interest. If exposure is the basis for selection, exposure patterns in the population must be adequately characterized in advance; if effects are the basis, the quality of pertinent diagnostic information is an issue. Selection of study populations is an integral part of a research strategy and of study design, and strategic concerns sometimes dominate the selection process.

The air pollution effect that is sought might be virtually undetectable in the presence of more powerful risk factors, which could make it appropriate to study individuals or groups that lack these factors. Examples of this approach include the study of young children to avoid confounding by smoking or by occupational exposures and the study of long-term residents to avoid confounding by residential mobility. Exclusion of (and thus, control for) confounding factors through subject selection eliminates the possibility of gaining information about interactions between these factors (e.g., smoking) and the ambient air pollutants under study. If air pollution and other factors, such as smoking, interact synergistically (i.e., multiply each other's effects), smokers might well be the group in which the most cases of pollution-related disease occur and therefore the group in which it is easiest and most important to detect it.

The use of sensitive populations in a study can also be deliberate. Human sensitivity to deleterious factors tends to vary widely, and our ability to detect effects when they are present is considerably sharpened when we can identify and focus on a population that has a steep dose-response curve. The response of highly susceptible people to specific magnitudes of air pollution is assumed to predict the response of average people to greater magnitudes. Asthmatics, bronchitics, children, the elderly, and subjects with cardiopulmonary diseases have long been considered to be sensitive to air pollutants. As Chapter 2 pointed out, the biologic nature of this presumed hypersusceptibility is not well understood, and much more information from all types of studies is needed for the characterization of sensitive populations. Investigators must know which sensitive populations are needed for which research questions and must have ways of determining whether a given person is a member of the population needed. Initial screening of a population might even be necessary to ensure that the desired sensitivity characteristic is present, particularly if the characteristic--such as atopy (a hereditary predisposition toward developing allergic reactions) or bronchial hyperreactivity--cannot easily be identified with routine clinical data.[6]

VOLUME OF DATA AND DATA REDUCTION

It is characteristic of air pollution epidemiology that large amounts of data are produced. These data must be reduced to manageable proportions, and that requires attention early and often in each major phase of a study--design, performance, analysis, and reporting. Methods of data reduction are diverse and include selection of smaller subsets for some studies, making continuous data discrete (e.g., creating a dichotomy), averaging (e.g., of repeated measures across time), and statistical modeling (including rate-of-change models). The following are examples of data reduction in air pollution studies:

- Reduction of semicontinuous ozone data to peak exposures and time-weighted averages for each year of study (reduction could still leave several dozen ozone measurements).

- Setting aside* of data on nonasthmatics (persons presumed to have low sensitivity to the agent in question)--i.e., reduction of their influence on the results to zero.

- Reduction of complex cigarette-smoking histories to numbers of pack-years.

- Reduction of asthma data to number of episodes per year.

Profound and difficult issues must be addressed in deciding which data items to collect and, once they are collected, which to reduce (and how) and which to set aside. Inappropriate data reduction can negate the careful selection and matching of exposure, confounder, and effect variables. Those who make decisions about data reduction should be thoroughly familiar with the overall design and purposes of their study.

Large volumes of data inevitably entail dilution of resources and attention, so data quality might be inversely related to data quantity. Even if the cost of collecting another item or two on each subject is small, the possible erosion of quality militates against the collection of any data that cannot be used to advance the main objectives of the study. Of course, changes in budgets and new research reports that arrive during the study period can dictate changes in the basic data to be collected.

MULTIPLE ANALYSES

Multiple tests and large data volume in air pollution studies also entail multiple statistical procedures and drawing of multiple conclusions. Two serious and related problems in data analysis and interpretation are multiple comparisons and after-the-fact hypotheses. The problem of multiple comparisons is well recognized. When a large series of statistical tests of significance are performed, the probability that one or more of them will be outside the arbitrary level of statistical significance (usually < 0.05) will be larger than that arbitrary level itself--perhaps much larger. The p value represents the probability that a positive result could have been achieved by chance alone. A p value of 0.05 corresponds to a 5% chance of such a false-positive result; if one conducts 100 statistical tests on the data, about 5 positive results can be expected, regardless of the true biologic relationships involved. The multiple-comparisons problem is present whether one is testing the same hypotheses over and over or testing many hypotheses once each.

---

*We note a preference for the idea of setting aside data not used in a particular analysis, as opposed to discarding such data. Data are in fact rarely discarded (nor should they be) as long as there is still some thought that they might be useful for some other, future purpose.

The problem of multiple comparisons is compounded because the multiple tests might not all be reported in the same publication, and many might not be reported at all. Some might not even be formally and explicitly performed, if quick inspection shows that results are not likely to be "interesting." One might perform tests only if preliminary study shows a likelihood of "positive" results. The problem of untested or unreported hypotheses, sometimes referred to as the "file-drawer problem," can plague the interpretation of air pollution studies.

One who is attempting to evaluate a reported positive result of an epidemiologic study is usually unaware of whether the positive relationship stemmed from a hypothesis developed before or after preliminary analysis. Given the risks of false-positive results due to chance, a before-the-fact hypothesis that yields a positive result obviously carries more weight than one that appears after exhaustive review of the data. By specifying in advance the major hypotheses that they wish to test, investigators can greatly add to the confidence in their positive results.

The purpose of the foregoing discussion is not to discourage the thorough exploration of large data sets, nor the reanalysis of old ones, but rather to point out to those concerned with air pollution epidemiology that multiple analyses of large data sets carry certain perils to interpretation and that these perils can be mitigated during study planning.

MULTIVARIATE MODELS

Contemporary epidemiologic studies of air pollution usually take a multivariate approach to analysis, because several confounding variables need to be controlled for simultaneously. Great advances have been made in the last 20 years in the application of powerful multivariate statistical techniques to epidemiologic data. However, major problems can be encountered when these approaches are used, particularly with large volumes of data. There is sometimes a tendency to use these sophisticated techniques in an unsophisticated way--i.e., to compensate for inadequacies in the data. In general, a multivariate model can be no better than the data put into it; nonrandom error is likely to occur in air pollution studies and is especially resistant to statistical treatment.

Collinearity--the correlation of important variables with each other--leads to other problems. The presence of large correlations between variables lessens the opportunity to attribute effects to any particular predictor variable, including exposure to specific air pollutants. Concentrations of specific pollutants tend to vary together. Loading of models with too many variables, especially ones that do not convey information not inherent in the others, can sometimes cause overcorrection, or overadjustment, and keep a real effect from being detectable. This can be understood as a result of mincing the data into so many small stratified bits that the statistical power of the study is seriously diminished. Statistical techniques alone cannot compensate for limitations imposed by collinearity in an air pollution data set. Fortunately, new techniques can be used at least to determine the extent of the collinearity problem in a particular study.

Multivariate models can be used in two distinct ways: to explain the relationships among exposure, effect, and confounding variables within the data set; and to extrapolate beyond the range of the data, to permit predictions for situations with different magnitudes or conditions of exposure. In the latter use, with no actual data for guidance, the results of extrapolation depend on the nature of the chosen model. Even within a study, adoption of a biologically incorrect model can lead to false inferences about the presence or absence of an association. The choice of possible models is usually wide. Some, such as the multistep theory of carcinogenesis, are based on presumptions about biologic mechanisms of action; others, such as models that relate pollutant concentration to tissue dose, are concerned with toxicokinetics. Most model formulations have no biologic basis other than intuitive plausibility. The biologic uncertainty is usually so great that many epidemiologists are beginning to perform analyses on several models routinely. The differences in estimates of association or risk that are produced reflect an important source of uncertainty. Sensitivity analysis provides a new technique for estimating the sensitivity of a given epidemiologic result to model specification.[8]

Multivariate analyses of air pollution data have not always searched for effects due to interactions between variables, as opposed to effects due to single variables. In the simplest case, two pollutant measures, or one pollutant and one confounder, can produce an effect when present together, but no effect when present alone. Such interactions might be important in air pollution studies and should be tested through statistical modeling whenever possible. Goldsmith and co-workers have recently used path analysis, a more highly structured type of linear regression, to analyze data on pollution concentrations and daily emergency-room visits in Los Angeles.[2] This technique requires the investigators to create models that specify the relations among variables in a more detailed and structured manner than conventional multivariate analysis. It could lead to improvements in separating the effects of specific exposure variables, particularly in ecologic studies.

COMBINING RESULTS FROM INDEPENDENT STUDIES

Epidemiologists have a special interest in the combination of results from independently conducted studies. Results of individual studies are not likely to be definitive on a particular research question and require interpretation within the context of similar work. In addition, several studies often show a negative result or a statistically nonsignificant association, but by themselves lack the statistical power (usually owing to insufficient sample size) to detect small effects. Sometimes, multiple analyses produce inconsistent conclusions. An inconclusive result and a positive result are generally not difficult to reconcile, but two conclusive results in "opposite" directions can present serious problems--in policy and regulation, as well as in science. Epidemiologic studies, when they are based on observation of natural phenomena, are not repeatable in a strict sense. The data analyst must attempt to reconcile conflicting results by further study and usually more convoluted methods of analysis. Alternatively, there are forums--such as criteria documents, committee reports, and review articles--that allow for expert subjective judgment on the strengths and weaknesses of individual studies and the overall direction of the evidence.

Environmental health researchers have become interested in formal techniques for combining evidence. Some are based on Bayesian principles of subjective probability and analyses of decision under uncertainty.[14] Meta-analysis, a more formal procedure, treats results from groups of independently conducted studies in a statistical manner.[10 13] Although meta-analysis is seductively simple, it contains serious perils when applied to most epidemiologic studies, and its quantitative nature can mask serious flaws in data. In essence, meta-analysis assumes that the results of studies can themselves be treated as random variables with predictable distributions. That assumption might be reasonable for experiments repeated under very similar conditions, but it is rarely so for epidemiologic studies, in which extraneous factors are harder to control and nonrandom errors dominate the random ones. Weighting studies according to such features as data quality can also be treacherous. Moreover, for meta-analysis to work, it must be assumed to include all or a representative sample of all studies on a particular question. The possible existence of an unknown number of multiple comparisons, in file drawers or in the minds of researchers, makes this a dubious assumption as well, although procedures have been developed to calculate the number of unretrieved studies that would be required to alter a combined-probability estimate.[11] The pooling of observations from independent studies to increase sample size is questionable in environmental epidemiology, because it ignores the differences between studies altogether. Numeric combination of results from different studies still has only a small role in epidemiology.

INDIVIDUAL REGRESSIONS

Logit, or individual regression analysis, a powerful new approach to the analysis of small-cohort (panel) data on air pollution and disease occurrence over time, uses a multiple logistic model to predict each subject's probability of having an asthmatic attack or some other adverse event in a given period. Previous methods, most commonly used in asthma studies, had relied on the panel attack rate as the outcome variable and had constructed models to predict this rate. The panel attack rate is defined as the number of panelists reporting an attack on a given day divided by the total number of panelists reporting. Interindividual differences in response to pollutants are such that this grouped outcome variable obscures the useful information embedded in the observations.

Whittemore and Korn reanalyzed part of a previously collected data set and, on the basis of individual probabilities, improved the adjustment for confounders and increased the power of the data set for detecting small effects.[15] It was also possible to adjust for temporal autocorrelation, in which the best predictor of an asthmatic attack on a given day is the occurrence of an attack on the previous day. Much of the power of this approach stems from each person's constituting an experiment over time while serving as his or her own control. The incorporation of individual, rather than grouped or aggregate, data into these types of studies, with refinements in the exposure and effect data themselves, will yield some promising avenues for research. It might be possible, given enough days of observation, to conduct highly sensitive epidemiologic studies on acute-effect questions with only a small sample of subjects.

INFERENCE AND CAUSALITY

Once questions have been formulated, the practice of epidemiology is a sequential process of assembling bits of information into a body of evidence and using inductive reasoning to draw inferences from it. A few points about the nature of epidemiologic reasoning, particularly the inference of causality, must be understood.

Epidemiologic reasoning has two fundamental characteristics: it deals with units of observation (rates of disease in populations) that are larger and less perceptible than events that are directly observable, such as cancer seen in a microscope, a spike on a chart recorder, or a color in a test tube; and it is normally based on the observation of natural events, rather than on the results of experimental manipulation.

The first characteristic is not peculiar to epidemiologic inquiry. Most branches of science have progressed far beyond the point where two events must be directly observed if they are to be causally linked. Hume recognized 250 years ago that causality in science is, in a sense, always inferred: "We are never able, in a single instance, to discover any power or necessary connection, any quality which binds the effect to the cause, and renders one the infallible consequence of the other."[5] Positive (or negative) findings in either observational or experimental research are therefore statistical associations, which can always be explained in any of three ways: they reflect causality, they reflect a noncausal relation, or they reflect chance. Epidemiologic reasoning does not stop at the demonstration of a statistical association, but goes on to "the practical purpose of discovering (causal) relations which offer possibilities of disease prevention."[7] (Bias, confounding, and chance--the three main determinants of the truth, or validity, of a given study--have already been discussed.)

Noncausal or spurious associations that emerge from epidemiologic studies must be distinguished from indirect associations. Indirect associations occur when a third factor is an intermediate or intervening variable in the causal chain between the primary two. Indirect associations are the rule, rather than the exception, in epidemiology (particularly air pollution epidemiology), because the exposure, as measured, is rarely the ultimate or direct cause of the adverse effect. Advances in knowledge tend to reveal successively deeper layers of causality, like the wooden Russian dolls that nest within one another. To take a hypothetical example, an association between adverse health effects and particles might be found to be due to aerosol sulfates, then to hydrogen ions, and eventually to interactions between hydrogen ions and ozone. We must emphasize that an indirect association can be a basis for preventive action, as long as changing the indirect causal factor results in the desired change in the occurrence of disease.

Over the last 25 years, epidemiologists have developed a set of guidelines for judging whether statistical associations derived from observational studies truly reflect causality. These guidelines, which apply equally to inference from a single study and to inference from a set of similar studies, are as follows:

- Strength (magnitude) of the association: The larger the calculated relative risk, the greater the likelihood that the observed association is causal. Relative risks of illness due to air pollution are likely to be small.

- Consistency (reproducibility): Causal inferences are strengthened when a variety of investigators have reproduced the findings under a variety of circumstances.

- Sequence of events: Inferences are strengthened when it is clear that exposure preceded illness, rather than vice versa.

- Biologic gradient of the association (dose-response relationship): If an exposure is causally related to an illness, the risk of developing the illness or its severity should be related, in a graded fashion, to the magnitude of exposure. Occasionally, a confounding variable may be so closely linked with exposure that they share the same dose-response relation to the illness and cannot easily be separated.

- Specificity of the association: Causality is more likely if a particular exposure is associated with only one illness and vice versa. This guideline rarely applies to air pollution research, in which all the diseases of major concern are multifactorial.

- Biologic plausibility of the association: An epidemiologic inference of causality is greatly strengthened when it conforms to knowledge concerning the biologic behavior of a toxin and its mechanism of action. This evidence may be obtained from clinical research or toxicologic studies.

The greatest possible assurance of a causal relationship can be obtained by finding that the rates of illness in a population change in a consistent manner after a change in exposure. Opportunities to observe such related changes sometimes occur naturally and in rare instances can be studied by experiment or intervention. Sometimes, however, too great a distinction is made between causal inference from observational studies and that from experimental studies--as though the evidence provided by the two were qualitatively different. The difference between the two lies in the greater ability of experimental research to control extraneous variables, and not in the inherent quality of the associations it finds.

The final step in the inferential process in epidemiology requires the extension of a study's results to persons, populations, or settings not specifically included in the study. The confidence with which this is done for positive results is usually based implicitly on how successful the investigators have been in identifying and handling the factors that produce or influence the pollution-effect association they have observed, including sampling variation. Whether and how the conditions studied are special can then be judged. Inferring from negative studies must be a good deal more cautious, because, as it is sometimes said, it takes a nearly infinitely large sample to conclude that a particular association cannot be found somewhere, under some set of circumstances.[4]

REFERENCES

1. Bates, D.V., and B. Sizto. Relationship between air pollutant levels and hospital admissions in southern Ontario. Can. J. Pub. Health 74:117-122, 1983.

2. Goldsmith, J.R., H.L. Griffith, R. Detels, S. Beeser, and L. Neumann. Emergency room admissions, meteorologic variables, and air pollutants: A path analysis. Am. J. Epidemiol. 118:759-778, 1983.

3. Groupe Cooperatif PAARC. Air pollution and chronic or repeated respiratory diseases: II. Results and discussion. Bull. Eur. Physio-pathol. Respir. 18:101-116, 1982.

4. Hernberg, S. Evaluation of epidemiologic studies in assessing the long-term effects of occupational noxious agents. Scand. J. Work Environ. Health 6:163-169, 1980.

5. Hume, D. Treatise on Human Nature. Selby-Bigge, Ed. Oxford: Clarendon, 1896. 709 pp.

6. Jones, R.N., B.T. Butcher, Y.Y. Hammad, J.E. Diem, H.W. Glindmeyer, III, S.B. Lehrer, J.M. Hughes, and H. Weill. Interaction of atopy and exposure to cotton dust in the bronchoconstrictor response. Br. J. Ind. Med. 37:141-146, 1980.

7. MacMahon, B., and T.F. Pugh. Epidemiology: Principles and Methods. Boston, Mass.: Little, Brown Publishing Co., 1970. 376 pp.

8. Osborn, J.F., and P. Armitage. Statistical Methods in Medical Research. New York: Blackwell Scientific Publications, 1979. 154 pp.

9. Pengelly, L.D., A.T. Kerigan, C.H. Goldsmith, and E.M. Inman. The Hamilton study: Distribution of factors confounding the relationship between air quality and respiratory health. J. Air Pollut. Control Assoc. 34:1039-1043, 1984.

10. Rosenthal, R. Combining results of independent studies. Psychol. Bull. 85:185-193, 1978.

11. Rosenthal, R. The "file drawer problem" and tolerance for null results. Psychol. Bull. 3:638-641, 1979.

12. Sackett, D.L. Bias in analytical research. J. Chron. Dis. 32:51-63, 1979.

13. Strube, M.J., and D.P. Hartmann. A critical appraisal of meta-analysis. Br. J. Clin. Psychol. 21:129-139, 1982.

14. Thomas, D., J. Siemiatycki, R. Dewar, J. Robins, M. Goldberg, and B. Armstrong. The problem of multiple inference in studies designed to generate hypotheses. Am. J. Epidemiol. 120:503, 1984.

15. Whittemore, A.S., and E.L. Korn. Asthma and air pollution in the Los Angeles area. Am. J. Pub. Health 70:687-696, 1980.